Draft

Report on Carcinogens
Background Document for

Beryllium and Beryllium Compounds

December 16 - 17, 1999

Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee

Prepared for the:
U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program
Research Triangle Park, NC 27709

Prepared by:
Technology Planning and Management Corporation
Canterbury Hall, Suite 310
4815 Emperor Blvd
Durham, NC 27703
Contract Number NOI-ES-85421

Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

Beryllium and Beryllium Compounds

Beryllium and beryllium compounds were first listed in the Second Report on Carcinogens as *reasonably anticipated to be human carcinogens*

Carcinogenicity

Beryllium and beryllium compounds are *known to be human carcinogens*, based on findings of increased risk of lung cancer in occupational groups exposed to beryllium or beryllium compounds (Steenland and Ward 1991; Ward *et al.* 1992) and supporting animal data (IARC 1993; Finch *et al.* 1996). The epidemiologic evidence supports a conclusion that beryllium and beryllium compounds are carcinogenic to humans. An association with lung cancer has been consistently observed in several populations, with an excess risk of 1.2 to 1.6. Higher risks are found in groups with greater exposure or longer time since first exposure, which are dose-response patterns that support a causal relationship. Acute beryllium pneumonitis, a marker for high exposure to beryllium, is associated with elevated lung cancer rates, with an excess risk of 2.3 (Steenland and Ward 1991). Although smoking is a potential confounder, no evidence was found in any of the published epidemiology studies to indicate that the prevalence of smoking in any of the exposed cohorts was substantially greater than in the referent populations.

Animal experiments have shown consistent increases in lung cancers in rats, mice and rabbits chronically exposed to beryllium and beryllium compounds by inhalation or intratracheal instillation. Osteosarcomas have been produced in mice and rabbits exposed to various beryllium salts by intravenous injection or implantation into the bone.

Other Relevant Information

Beryllium compounds were not mutagenic in a variety of *Salmonella* tester strains. However, beryllium compounds induced genetic transformations in a variety of mammalian cells, *in vitro*. The genetic transformation effects of beryllium may be mediated by binding of ionic beryllium to nucleic acids that can produce infidelity in DNA replication.

Table of Contents

List of Tables

List of Figures

1 Introduction

Beryllium and certain beryllium compounds were first listed in the National Toxicology Program's (NTP) Second Annual Report on Carcinogens in 1981 as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity in experimental animals and limited evidence in humans. Beryllium and beryllium compounds were nominated for possible upgrading to *known to be human carcinogens* based on the publication of an International Agency for Research on Cancer (IARC) monograph (1993) which stated that beryllium and beryllium compounds are carcinogenic to humans (Group 1) based on sufficient evidence of carcinogenicity in humans and experimental animals.

1.1 Chemical identification

Elemental beryllium (mol wt 9.01218, CASRN 7440-41-7) is a hard, grayish metal. It is also known as beryllium metal, beryllium-9, beryllium metallic, glucinium, or glucinum. It is one of the lightest of all metals and has one of the highest melting points of the lightest metals. Beryllium occurs naturally as a chemical component of certain kinds of rock, such as bertrandite, beryl, beryl ore, chrysoberyl, and phenakite. It also is found as a component of coal, soil, and volcanic dust. Some of the beryllium compounds discussed in the present review include the following:

beryllium-aluminum alloy
beryllium-copper alloy
beryllium-nickel alloy
beryl ore
bertrandite
chrysoberyl
beryllium acetate
beryllium carbonate
beryllium chloride
beryllium fluoride
beryllium hydroxide
beryllium nitrate
beryllium silicate
beryllium sulfate
beryllium oxide
beryllium phosphate
beryllium zinc silicate.

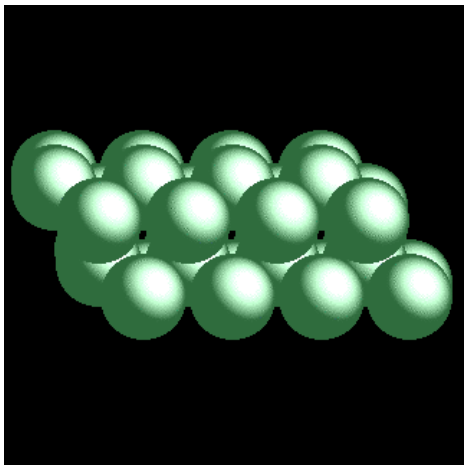
The U.S. Environmental Protection Agency (EPA) codes are K061 for beryllium and P015 for beryllium compounds. Shipping codes are UN1567 for beryllium and 1566 Poison B for beryllium compounds.

1.2 Physical-chemical properties

The structure of Beryllium is hexagonal close-packed, as illustrated in Figure 1-1. Beryllium has a very high specific heat, heat of fusion, sound conductance, and strength-to-weight ratio. Beryllium is lighter than aluminum but is > 40% more rigid than steel. Beryllium's modulus of elasticity is about one third greater than that of steel. It has excellent thermal conductivity and is non-magnetic. At ordinary temperatures, beryllium resists oxidation in air; however, its ability to scratch glass is probably due to the formation of a thin layer of the oxide.

Alloys are substances composed of two or more metals, or sometimes a metal and a non metal, which have been mixed intimately by fusion, electrolytic deposition, or other

means. Beryllium in alloys contributes hardness, strength, and high electrical and thermal conductivity; it confers enhanced resistance to corrosion, wear, and fatigue. Beryllium alloyed with copper, aluminum, and other metals is used in the electronics, automotive, defense, and aerospace industries. Beryllium alloys also are used in dental applications and sporting goods (U.S. DOE 1999).



Source: WebElements2000 (1999)

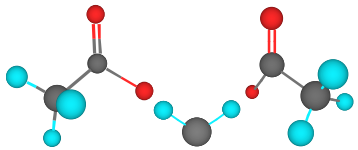
Figure 1-1. Structure of beryllium

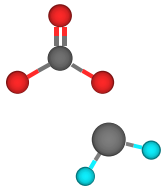
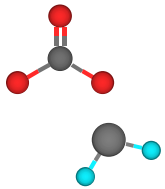
The physical and chemical properties of elemental beryllium and its compounds are listed in Table 1-1 and Table 1-2, respectively.

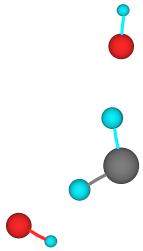
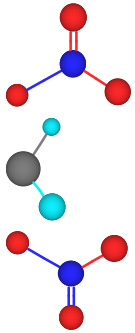
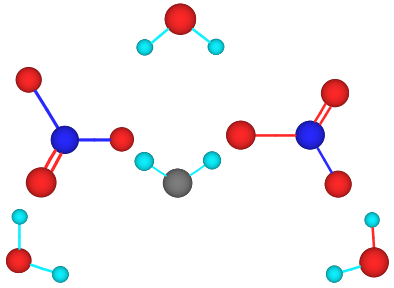
Table 1-1. Physical and chemical properties of elemental beryllium

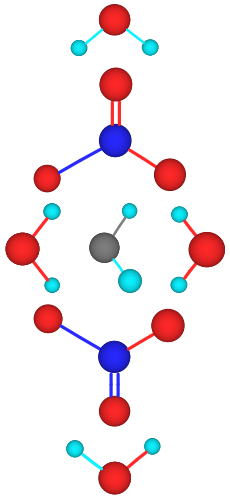
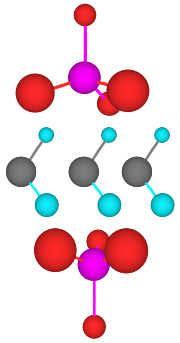
Property	Information	Reference
Molecular weight	9.01218	Budavari *et al.* (1996); CRC (1998)
Color	silvery, resembles aluminum powder	Budavari *et al.* (1996); CRC (1998)
Odor	odorless	CRC (1998)
Physical state	solid	Budavari *et al.* (1996); CRC (1998)
Melting point (°C)	1287	Budavari *et al.* (1996); CRC (1998)
Boiling point (°C)	2970	Budavari *et al.* (1996); CRC (1998)
Density (g/cc at 20 °C)	1.844	Budavari *et al.* (1996); CRC (1998)
Crystal system	hexagonal close-packed	Yang and Coppens (1978)
Young's modulus (psi)	44 x 106	Rossman *et al.* (1991)
Solubility in: Water at 20°C Acids (dilute) Alkalies (dilute)	 insoluble soluble soluble	Budavari *et al.* (1996); CRC (1998); HSDB (1998)

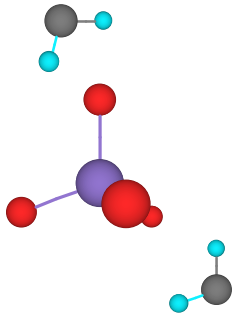
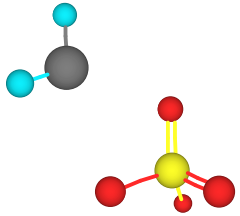
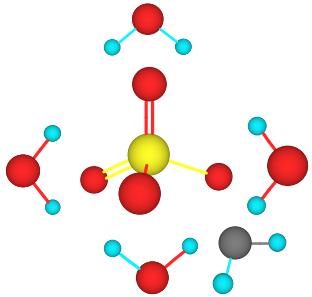
Table 1-2. Physical and chemical properties of beryllium compounds[a]

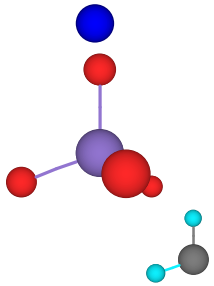
Compound	CASRN	Structure	mol wt	Physical state	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility	Decomposition products upon heating
Beryllium-aluminum alloy 62% Be, 38% Al	12770-50-2	NR	NR	NR	NR	NR	NR	NR	toxic fumes of BeO
Beryllium-copper alloy 0.3 - 2.0% Be, 96.9 - 98.3% Cu; 0.2% min. Ni and Co, 0.65 max. Ni, Fe, and Co	11133-98-5	NR	NR	NR	870-980	NR	NR	NR	toxic fumes of BeO
Beryllium-nickel alloy 2-3% Be; up to 4% other additives; rest Ni	37227-61-5	NR	NR	NR	NR	NR	NR	NR	NR
Beryl ore $[Be_3(AlSi_3O_9)_2]$ 2.03% Be, 10.04% Al, 31.35% Si, 53.58% O	1302-52-9	NR	537.502	blue-green, yellow, or white, transparent hexagonal crystal	1650	NR	2.80[b]	insoluble in acid.	NR
Chrysoberyl $[BeAl_2O_4]$ 7.10% Be, 42.5% Al, 50.4% O		NR	126.973	green, yellow, or brown orthorhombic crystal	NR	NR	3.75[b]	NR	NR
Beryllium acetate $C_4H_6BeO_4$	543-81-7		127.10	colorless plates	300 (decomposes)	NR	NR	insoluble in cold water, ethanol, and other common organic solvents slow hydrolysis in boiling water	NR

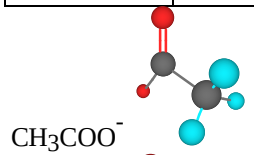
Compound	CASRN	Structure	mol wt	Physical state	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility	Decomposition products upon heating
Beryllium carbonate $BeCO_3$	66104-24-3		69.021	NR	NR	NR	NR	soluble in acids and alkali, insoluble in cold water, decomposes in hot water.	NR
Beryllium carbonate; Carbonic acid, beryllium salt (1:1) $BeCO_3$•$Be(OH)_2$	13106-47-3		112.05	white powder	NR	NR	NR	soluble in acids and alkali, insoluble in cold water, decomposes in hot water.	NR
Beryllium chloride $BeCl_2$	7787-47-5		79.918	white to colorless deliquescent needles	405[c]	520[c]	1.899[c] (25°C)	soluble in water, alcohol, benzene, ether, and pyridine slightly soluble in chloroform and benzene. insoluble in acetone. insoluble in ammonia.	toxic fumes of BeO, HCl and other chlorinated compounds.
Beryllium fluoride BeF_2	7787-49-7		47.009	colorless amorphous mass	545[c] (800 sublimes)	1,160[c]	1.986[c] (25°C)	readily soluble in water. slightly soluble in sulfuric acid and alcohol.	toxic fumes of BeO, HF and other fluorinated compounds

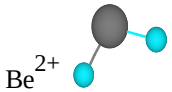
Compound	CASRN	Structure	mol wt	Physical state	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility	Decomposition products upon heating
Beryllium hydroxide $Be(OH)_2$	13327-32-7		43.027	three crystal or powder forms metastable tetragonal crystalline solid stable orthorhombic crystalline solid in slightly basic pH appears as a slimy, gelatinous substance	138[c] decomposes to BeO	NR	1.92[c]	slightly soluble in water[g]. soluble in hot concentrated acids and alkalies.	toxic fumes of BeO
Beryllium nitrate $Be(NO_3)_2$	13597-99-4		133.022	deliquescent crystalline mass	60	NR	NR	very soluble in water and alcohol.	NR
Beryllium nitrate trihydrate $Be(NO_3)_2{\cdot}3H_2O$	7787-55-5		187.068	white yellow deliquescent crystalline mass	60.5[e]	142[e]	1.,557[e]	very soluble in water and ethanol.	NR

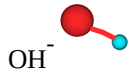
Compound	CASRN	Structure	mol wt	Physical state	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility	Decomposition products upon heating
Beryllium nitrate tetrahydrate $Be(NO_2)_3{\bullet}4H_2O$	13510-48-0		205.083	NR	NR	NR	NR	NR	NR
Beryllium oxide BeO	1304-56-9		25.0116	white amorphous powder or gel	2530	3787	3.016	0.2 mg/L (30°C) in water. soluble in acids, alkalies, and ammonium carbonate.	toxic fumes of BeO
Beryllium phosphate $Be_3P_2O_8$	13598-15-7		216.979	NR	NR	NR	NR	slightly soluble in water.	NR

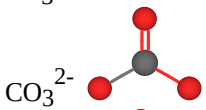
Compound	CASRN	Structure	mol wt	Physical state	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility	Decomposition products upon heating
Beryllium silicate Be_2SiO_4	13598-00-0		110.11	triclinic colorless crystals	1560[e]	NR	3.0	NR	NR
Beryllium sulfate $BeSO_4$	13510-49-1		105.07	colorless tetragonal crystals	decomposes 550 - 600[d]	Not applicable	2.443[d]	insoluble in cold water and alcohol, converts to tetrahydrate in hot water.	toxic fumes of BeO and sulfur oxides SO_x
Beryllium sulfate tetrahydrate $BeSO_4.4H_2O$	7787-56-6		177.13	colorless tetragonal crystals	100 (loses $2H_2O$)[d] anhydrous 270[e]	400 (loses $4H_2O$)[d] decom-poses 580[e]	1.713	insoluble in ethanol slightly soluble in concentrated sulfuric acid	toxic fumes of BeO and sulfur oxides SO_x

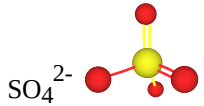
Compound	CASRN	Structure	mol wt	Physical state	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility	Decomposition products upon heating
Zinc beryllium silicate BeO_4SiZn	39413-47-3		166.49	crystalline solid	NR	NR	NR	NR	NR

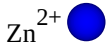


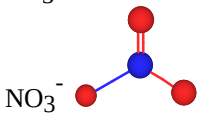


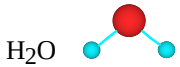


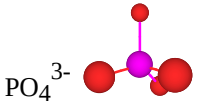


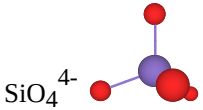












[a] All information obtained from Chemfinder (1998) except where noted.
NR: not reported.
[b] Emsley (1998).
[c] WHO (1990).
[d] Sax and Lewis (1987).
[e] Dean (1992).

1.3 Identification of metabolites

Beryllium metabolites *per se* have not been identified or studied. Snow (1992), however, reviewed effects of beryllium and beryllium compounds on cellular immunity and nucleic acid metabolism. This analysis compared beryllium with the carcinogenic metals, nickel and chromium. It was suggested that insoluble beryllium, engulfed by activated phagocytes, can be ionized by myeloperoxidases. Reactive oxygen intermediates formed in this inflammatory reaction to beryllium can bind to nucleic acids and interfere with the fidelity of DNA synthesis (Lansdown 1995, Leonard and Lauwerys 1987) (see section 6).

2 Human Exposure

2.1 Use

Beryllium is an extremely light metal with a very high melting point. Because of its unique properties, beryllium has many practical uses in industry. When used in alloys, it confers its unique properties, increasing thermal and electrical conductivity and strength (WHO 1990). Addition of only 2% of beryllium to copper forms alloys that are six times stronger than copper alone (LLNL 1997). Beryllium alloys find limited use in industry because of the low solubility of most other metals in solid beryllium, making alloys difficult to make or very brittle (WHO 1990).

Table 2-1 summarizes the uses for beryllium and beryllium compounds.

Table 2-1. Industrial uses for beryllium

Compound	Uses
Pure beryllium metal	Aircraft disc brakes, X-ray transmission windows, space vehicle optics and instruments, aircraft/satellite structures, missile parts, nuclear reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, mirrors
Beryllium oxide	High-technology ceramics, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armor, rocket nozzles, crucibles, thermocouple tubing, laser structural components
Beryllium alloys	Electrical connectors and relays, springs, precision instruments, aircraft engine parts, non-sparking tools, submarine cable housings and pivots, wheels, pinions, automotive electronics, molds for injection molded plastics for automotive, industrial and consumer applications

Source: LLNL (1997), WHO (1990), and ATSDR (1993).

2.1.1 Beryllium

Beryllium's earliest application was as a window for X-ray tubes. Because beryllium is relatively transparent to X-rays, these tubes were of the highest standard. Beryllium was then used in aircraft brake manufacturing because of its high specific heat (four times that of steel). Beryllium has a low density yet is very stiff, which results in dimensional stability. Because of these unique properties, it is used in missile, aircraft, and spacecraft guidance systems. Beryllium also is used in test reactors, tokamak reactors, and fusion reactors because it has a combination of high neutron multiplication, low absorption, and high scattering characteristics (Rossman *et al.* 1991).

2.1.2 Beryllium-copper alloy

Around 72% of all beryllium is used to produce beryllium-copper alloys (WHO 1990). While the alloy retains copper's desirable properties (corrosion resistance and thermal and electrical conductivity), addition of beryllium significantly increases the strength of the alloy. Few, if any, other types of copper alloy exhibit as great an increase in strength as beryllium-copper alloy. Because of the strength of this alloy, it can be used in many demanding applications, from military and commercial landing gear to oil field drill collars and drilling bit friction bushings (Rossman *et al.* 1991). Beryllium-copper alloys do not spark and are nonmagnetic. Non-sparking tools made of beryllium-copper alloy can therefore be used in explosive environments where sparks from steel-to-steel contact must be avoided (IARC 1993).

2.1.3 Other beryllium alloys

Beryllium-aluminum alloys have garnered increased attention particularly in the aerospace industry, because they are extremely lightweight, yet very strong (IARC 1993) (WHO 1990).

Beryllium-nickel alloys are used in some high-temperature applications because they have higher thermal conductivity and a greater hardness than beryllium-copper alloys (WHO 1990).

Beryllium-nickel-chromium alloys are used in dentistry as an alternative to gold because beryllium increases the porcelain-metal bond strength and facilitates castability (WHO 1990).

2.1.4 Beryllia ceramics

Beryllium oxide (BeO) ceramics exhibit many of the properties that are necessary for ceramic materials used in electronic packages. They are very effective electrical insulators, have the ability to be hermetically sealed, and have the mechanical properties suitable for mounting and protection of the electronic circuitry (Rossman *et al.* 1991). BeO ceramics have the highest thermal conductivity of the oxide ceramics. Together with their high heat capacity and electrical resistivity, this property allows BeO ceramics to be used as an electrical insulator in electronics and other applications that require thermal dissipation.

2.2 Production

Because of beryllium's increased importance in nuclear and aerospace technologies, U.S. production of beryllium has steadily increased. There are only two commercially important beryllium-containing minerals: beryl and bertrandite (Cunningham 1997).

Beryl ($3BeO \cdot Al_2O_3 \cdot 6SiO_2$), which contains around 11% beryllium oxide (up to 4% beryllium), is the predominant beryllium-containing mineral mined in the world. Beryl is found largely in Brazil and the former U.S.S.R. Impurities in beryl include alkali metals, alkaline-earth metals, iron, manganese, and phosphorus. Emeralds (chromium-containing

beryl), aquamarine (iron-containing beryl), and other semiprecious gems are examples of beryl at its purest gem quality (IARC 1993).

Bertrandite ($4BeO \cdot 2SiO_2 \cdot H_2O$) is the principal beryllium-containing mineral mined in the United States, accounting for approximately 85% of U.S. consumption. Bertrandite contains < 1% beryllium but can be efficiently processed into beryllium hydroxide.

Other compounds also are being studied to determine the commercial feasibility of extracting beryllium from them. Two main examples are phenakite ($2BeO \cdot SiO_2$) and chrysoberyl ($BeO \cdot Al_2O_3$). Phenakite is found in Canada, and chrysoberyl is found mostly in Texas (IARC 1993).

Table 2-2 shows the trend toward increased beryllium production (Cunningham 1997).

Table 2-2. United States production and use

Salient statistics	Metric tons of beryllium				
	1993	1994	1995	1996	1997[a]
Production, mine shipments	198	173	202	211	210
Imports for consumption, ore, and metal	8	53	32	20	45
Exports, metal	20	29	61	57	45
Consumption: apparent	183	198	198	204	205
Consumption: reported	196	174	227	234	230

Source: Cunningham (1997).
[a] Estimated.

2.3 Analysis

Analysis of beryllium started with spectroscopic, fluorometric, gamma activation, spectrophotometric, and automatic titrimetric techniques. Atomic absorption spectrometry currently is used to determine beryllium levels in biological and environmental samples. Inductively coupled plasma atomic emission spectrometry is now being used because of its high sensitivity and low level of interference (IARC 1993).

Table 2-3 defines analytical and detection limits for various assays to determine beryllium levels.

Table 2-3. Analytical procedures and detection limits for beryllium

Sample Matrix	Assay Procedure[a]	Limit of Detection	Reference
Aqueous samples, extracts, wastes	FLAA ICP (313 nm) GFAA	0.005 mg/L 0.3 μg/L 0.2 μg/L	U.S. EPA (1986a) U.S. EPA (1986b) U.S. EPA (1986c)
Oil, greases, waxes (organic extract)	FLAA ICP	0.005 mg/L 0.3 μg/L	U.S. EPA (1986a) U.S. EPA (1986b)
Sediments, sludges, soils	FLAA ICP (313 nm) GFAA	0.005 mg/L 0.3 μg/L 0.2 μg/L	U.S. EPA (1986a) U.S. EPA (1986b) U.S. EPA (1986c)
Tissue samples	FLAA	2 μg/L	Kleinman *et al*. (1989)
Urine	GFAA (untreated) GFAA (modify matrix with magnesium nitrate)	0.5 μg/L 0.05 μg/L	Angerer and Schaller (1985) Paschal and Bailey (1986)

Source: IARC (1993).
[a]FLAA: flame atomic absorption spectrometry; GFAA: graphite furnace atomic absorption spectrometry; ICP: inductively coupled argon plasma emission spectrometry.

2.4 Environmental occurrence

2.4.1 Soil

Beryllium is the 44th most abundant element in the Earth's crust (IARC 1993). Beryllium concentrations in the Earth's crust are estimated at 2.6 ppm.

Beryllium and beryllium compounds are widely distributed in soils. Through geochemical surveys, it is estimated that the lithosphere contains 6 mg Be/kg. Agricultural soils in the United States average 0.6 mg beryllium/kg (ranging from < 1 to 7 mg beryllium/kg). The rare geological sites that contain large deposits of beryllium evidently account for the relatively high overall lithospheric beryllium concentration (WHO 1990). Anthropogenic contributions to beryllium soil concentrations include coal ash and municipal waste combustor ash. Industrial waste also is a source of beryllium in the soil. Land burial is the most popular method of disposing of industrial waste generated from the processing or use of beryllium (ATSDR 1993).

In compliance with the Emergency Planning and Community Right-to-Know Act (EPCRA), 16 facilities reported their total beryllium land release as 47,428 lb. No underground injection values were reported (TRI 1996).

2.4.2 Water

Surface water concentrations of beryllium are usually in the nanograms per liter range. Seawater levels of beryllium are one tenth those of surface waters, varying from 3.5×10^{-8} to 22×10^{-8} ppm (Emsley 1998). Increased beryllium concentrations in water levels usually are due to industrial wastewater effluents (WHO 1990). Deposition of atmospheric beryllium also adds to water concentrations. However, the relative contributions of these sources cannot be assessed. Beryllium also can enter the water through the weathering of rocks and soils (ATSDR 1993).

The mean concentration of beryllium in 1,577 U.S. drinking-water samples was calculated at 190 ng/L (range 10 to 1,200 ng/L) (U.S. EPA 1980, cited in ATSDR 1993). A more recent survey of metals in the New York City drinking water did not detect any beryllium in the samples with a detection limit of 10 μg/L (10,000 ng/L) (Iwan 1987, cited in ATSDR 1993). U.S. EPA has set a standard where by the concentration of beryllium in drinking water may not exceed 4 μg/L.

In compliance with the EPCRA, 16 facilities reported their total beryllium water release as 32 lb (TRI 1996). The reportable quantity for release of beryllium into water is 1 lb.

2.4.3 Air

Although windblown dust and volcanic particles account for some of the natural atmospheric releases of beryllium, combustion of coal and fuel oil is the most likely source of environmental release. Coal combustion and fuel oil are estimated to account for 96% of the U.S. beryllium emission from all natural and anthropogenic sources. The average beryllium concentration in coal is between 1.8 and 2.2 μg/g of coal. Beryllium also occurs in the ash of many coals at concentrations of around 100 μg/g coal ash (IARC 1993). It is estimated that 10% to 30% of the beryllium contained in coal is released into the ambient atmosphere. Regulatory limits dictate that fuel oil can contain no more than 0.08 ppm beryllium. It is assumed that about 40% of beryllium contained in fuel oil is released into the atmosphere (ATSDR 1993).

The Toxic Release Inventory (U.S. EPA) listed 16 industrial facilities that produced, processed, or otherwise used beryllium in 1996. In compliance with EPCRA, 16 facilities reported their total beryllium air release as 1,254 lb (TRI 1996). The reportable quantity for release of beryllium into air is 1 lb.

Table 2-4 summarizes anthropogenic and natural sources of beryllium emissions into the atmosphere. The national emission standard for beryllium is 10 g/24 h per facility.

Table 2-4. Emissions of beryllium into the atmosphere

Emission source	Total U.S. production (10^6 metric tons/year)	Emission factor (g/ton)	Emissions (ton/year)
Natural			
Windblown dust	8.2	0.6	5
Volcanic particles	0.41	0.6	0.2
Total			**5.2**
Anthropogenic			
Coal combustion	640	0.28	180
Fuel oil combustion	148	0.048	7.1
Beryllium ore processing	0.008[a]	37.5[b]	0.3
Total			**187.4**

Source: ATSDR (1993; adapted from data provided by U.S. EPA 1987).
[a] The production of beryllium ore is expressed in equivalent tons of beryl; the emission factor of 23.5 is estimated. Production of 8,000 tons/year of beryl is equivalent to ≈400 tons/year of contained metal.
[b] Units are metric tons.

Atmospheric background concentrations of beryllium have been reported to be less than 0.1 and 0.2 ng/m^3. Air samples taken over 100 cities in the U.S. from 1964 to 1965 did not contain detectable amounts of beryllium. From 1977 to 1981, average air concentrations of beryllium were around the limit of detection (0.03 ng/m^3). From 1981 to 1986, beryllium concentrations at urban monitoring stations exceeded of 0.03 ng/m^3, ranging from 0.11 to 6.7 ng/m^3. Atmospheric concentrations of beryllium are higher around beryllium processing plants than in other areas. The concentration of beryllium in air near a Pennsylvania factory averaged 15.5 ng/m^3, with a maximum of 82.7 ng/m^3, whereas the background concentrations in several locations in the area averaged only 0.2 ng/m^3 (IARC 1993).

The average air concentration of beryllium in the United States is 0.03 ng/m^3, and the median concentration in cities is 0.2 ng/m^3. According to a survey by the National Air Surveillance Network, atmospheric concentrations of beryllium (between 1977 and 1981) were > 0.1 ng/m^3 in 50 U.S. cities, with the highest average being 0.4 ng/m^3 in Dallas, Texas, in 1979 (ATSDR 1993).

2.5 Environmental fate

2.5.1 Air

Beryllium is most likely emitted into the atmosphere as BeO. BeO is formed through ore processing (both bertrandite and beryl contain BeO) and in stack emissions in burning of coal and refuse. It is not known whether BeO reacts with sulfur or nitrogen oxides in the atmosphere. If this process does occur, wet deposition of beryllium will be accelerated. Rainwater in Fresno, California, contained beryllium (concentrations not quantified), indicating that transport of beryllium to soil and water occurs via wet transport (ATSDR 1993).

Stack emissions from coal combustion were studied to determine relative particle aerodynamic size, wind speed, and surface roughness. Most beryllium particles were of a

median aerodynamic diameter of < 2.5 μm (Gladney and Owens 1976, cited in ATSDR 1993), meaning that these particles could remain airborne for around 10 days.

2.5.2 Water

Concentrations of dissolved beryllium in natural waters are very low. The most likely reaction between beryllium compounds and water is hydrolysis to form beryllium hydroxide (BeOH), which has low solubility in the pH range of most natural water. Although other reactions might occur that would allow other, more soluble complexes to be formed, the pH range needed for these reactions is not found in most natural waters. Studies comparing sediment and water beryllium concentrations show that sediment has beryllium concentrations several orders of magnitude higher than water, indicating that beryllium is not present in a dissolved form in the water as insoluble complexes naturally settle into the sediment. However, at higher pH, soluble complexes could be formed, increasing solubility and mobility of beryllium in water (ATSDR 1993).

Beryllium will remain in ocean water for a few hundred years before it is removed from the aquatic phase through sedimentation or some other removal system (ATSDR 1993).

Bioaccumulation of beryllium in fish is not thought to occur, because uptake of beryllium from the water by aquatic animals is low. Though beryllium is toxic to warmwater fish in soft water, bioconcentration factors (BCFs) of 100 were reported in freshwater and marine plants, invertebrates, and fish. A BCF greater than 1,000 is required for significant bioaccumulation in aquatic organisms. BCFs for bottom-feeding animals may be higher. There is no evidence of beryllium biomagnification in food chains (ATSDR 1993).

2.5.3 Soil

Beryllium is expected to have low mobility in soil. Because of its similarity to aluminum, beryllium is thought to be adsorbed onto clay surfaces at low pH. Higher pH may result in increased mobility of beryllium in soils. Beryllium reactions that might occur in the soil are hydrolysis of soluble salts, anion exchange reaction, and complexation reactions with ligands present in the soil (ATSDR 1993).

2.6 Environmental exposure

Inhalation of beryllium resulting in lung deposition is the primary route of exposure. Over time, beryllium slowly enters the bloodstream and is eventually excreted by the kidneys. It takes months or years for inhaled beryllium to be removed by the body. Beryllium exposure also may occur if beryllium is ingested into the body through drinking water, contaminated foodstuffs, or smoking. Ingestion, however, is not thought to be an important mode of exposure, because only 1% of ingested beryllium enters the bloodstream. Dermal exposure can occur if beryllium enters through cuts in the skin (ATSDR 1993).

Whether through consumption of contaminated food or water or through inhalation, the entire U.S. population is exposed to beryllium. U.S. EPA and ATSDR have estimated the

daily beryllium intake for the general population from background environmental exposure to be 420 ng/day. People who work in beryllium manufacturing, fabricating, and reclaiming industries are exposed to higher levels of beryllium than the general public. Smokers also may be exposed to higher levels of beryllium, because cigarette smoke contains beryllium (ATSDR 1993).

2.6.1 Environmental sources of beryllium

Beryllium has been found in various foods and cigarettes. Table 2-5 summarizes food surveys done to determine beryllium concentrations.

Table 2-5. Beryllium concentrations in various foodstuffs

Food	Measurement	Value
Polished rice	dry weight (mg/kg)	0.08
Potatoes	dry weight (mg/kg)	0.17
Toasted bread	dry weight (mg/kg)	0.12
Tomatoes	dry weight (mg/kg)	0.24
Head lettuce	dry weight (mg/kg)	0.33
Beans	in ash (ppm)	0.01
Cabbage	in ash (ppm)	0.05
Hen eggs (yolk)	in ash (ppm)	0.01
Milk	in ash (ppm)	0.02
Mushrooms	in ash (ppm)	0.12
Nuts	in ash (ppm)	0.01 - 0.47
Tomatoes	in ash (ppm)	0.02
Baker's yeast	in ash (ppm)	0.02

Source: HSDB (1997)

Beryllium also was found in three brands of German cigarettes (0.47, 0.68, and 0.74 μg/cigarette) (WHO 1990). It is estimated that from 4.5% to 10% of the beryllium in a cigarette passes to the smoker through the tobacco smoke (HSDB 1997).

2.7 Occupational exposure

The highest levels of human exposure to beryllium are through occupational exposure. Occupational exposure may occur via inhalation or dermal contact if workers are exposed to beryllium dust or handle products containing beryllium. Occupational exposure may also lead to at-home exposure to beryllium through work garments. In personal monitoring studies in the workplace, it was noted that air concentration measurements from personal monitors mounted on clothing increased when the fabric load of beryllium increased (HSDB 1997).

As applications of beryllium and beryllium compounds have increased, more workers are exposed, from miners to workers at processing plants and factories that convert beryllium into alloys and chemicals. It has been estimated that over 800,000 workers have been exposed to beryllium (Cullen *et al*. 1986, cited in Meyer 1994). The National

Occupational Exposure Survey estimated that a total of 19,012 workers, including 1,778 women, might have been exposed to beryllium between 1980 to 1983 (NIOSH 1990). The following industries have the potential for occupational exposure to beryllium (WHO 1990):

ceramics
nonferrous foundries
sandblasting
nuclear control equipment
refractories
hazardous waste processing
engineering and scientific equipment
tool and die making
welding or flame cutting
automotive parts
golf club manufacture
electrical connectors
nonferrous smelters
aerospace
electronics
beryllium smelting or fabrication
dental equipment and supplies
mechanical measuring devices
soldering
metal plating
telecommunication equipment

2.7.1 Processing and manufacturing

Beryllium is released during the various processes involved in processing and manufacturing beryllium compounds. These include melting, casting, molding, grinding, buffing, welding, cutting, electroplating, milling, drilling, and baking (WHO 1990). Control measures were instituted in 1949 to limit high exposures to beryllium. In a sample of 2,627 air samples taken between 1950 and 1957, Breslin and Harris (1959, cited in IARC 1993) reported that 10% to 15% of the workers were exposed to beryllium concentrations greater than the standard Occupational Safety and Health Administration (OSHA) limit (2 $\mu g/m^3$).

Kriebel *et al*. (1988) calculated time-weighted average (TWA) air concentrations of beryllium in a U.S. refinery. This refinery is where most of the beryllium in the United States has been refined since 1934, with beryllium-copper alloys as its principal product. Before 1977, beryllium exposure levels at the plant were sometimes in excess of 100 $\mu g/m^3$. After 1977, exposure levels decreased so as not to exceed the permissible exposure level of 2 $\mu g/m^3$. Although there was some overlap in the plants surveyed, the median exposure for 297 white male workers in 1977 was 0.4 $\mu g/m^3$. The median cumulative exposure (with a mean of 17 years worked) was 65 $\mu g/m^3$ per year. Table 2-6 summarizes the data.

Table 2-6. Daily weighted average air concentrations (μg/m^3) of beryllium in a U.S. beryllium production plant for four time periods

Department	Approximate number of workers in 1943	Number of jobs in department	beryllium (air) concentration			
			1935–54	1955–64	1965–76	1977–83
Oxide	46	14	46	16	8.8	0.5
Arc furnace room	26	6	80	51	11	0.7
Detroit furnaces	24	4	51	51	33	NA
Foundry	27	5	19	19	13	NA
Melt and cast	105	6	18	18	7.6	1.1
Hot rolling	19	8	9.3	9.3	2.5	0.2
Cold rolling	29	8	9.2	5.7	2.5	0.2
Rod and wire	39	8	5.9	5.9	2.0	0.2
Annealing	10	5	13	13	5.7	0.1
Pickling	11	3	0.2	0.2	0.2	0.1
Machining, grinding	60	5	1.7	1.7	0.9	0.1
Maintenance	73	13	6.2	5.7	3.5	0.1
Inspection	12	7	1.6	1.6	0.9	0.1
Laundry	–	1	2.5	2.5	1.0	0.1
Laboratories, research and development	28	6	1.4	1.4	1.2	1.2
Store, shipping	20	3	3.6	3.6	2.0	0.1

Source: Kriebel *et al.* (1988, cited in IARC 1993).
NA = not applicable; these departments were not operational during 1977–83.

One of the most extensive studies done in the United States to determine occupational exposure levels of beryllium was the Rocky Flats Environmental Technology Sites (RFETS) studies. The RFETS are a part of the U.S. Department of Energy nuclear weapons complex. Beryllium use began in 1953, and beryllium production began in 1957. Barnard and Torma-Krajewski (1994, cited in Stange *et al.* 1996) analyzed two beryllium production buildings to determine beryllium levels between 1984 and 1986. From the random fixed-airhead samples from 1984 to 1986, the mean beryllium exposure level was 0.16 $\pm$ 0.33 μg/m^3 (95% CI = 0.10 - 0.22 μg/m^3). The mean beryllium exposure level in personal breathing-zone samples was 1.04 $\pm$ 1.25 μg/m^3 (95% CI = 0.79 - 1.29 μg/m^3). There was no correlation between the fixed-airhead and personal breathing-zone results (r^2 = 0.029). Table 2-7 summarizes the sampling data from the RFETS.

Table 2-7. Beryllium concentration in samples from two main beryllium production buildings at RFETS

Year	Fixed airhead		Personal breathing zone	
	Number of samples (random sample)	Mean (μg/m^3)	Number of samples	Mean (μg/m^3)
1970	308	0.306	–	–
1971	402	0.358	–	–
1972	430	0.358	–	–
1973	430	0.416	–	–
1974	416	0.228	–	–
1975	432	0.162	–	–
1976	431	0.105	–	–
1977	432	0.121	–	–
1978	431	0.134	–	–
1979	369	0.102	–	–
1980	410	0.156	–	–
1981	426	0.137	–	–
1982	432	0.163	–	–
1983	432	0.271	–	–
1984a	180	0.304	–	–
1984b	243	0.158	33	1.092
1985	396	0.163	51	1.195
1986a	242	0.159	33	0.779
1986b	48	0.039	29	0.092
1987	255	0.034	16	0.189
1988	310	0.045	–	–

Source: Barnard *et al*. (1996).

2.7.2 Machining

The National Institute of Occupational Safety and Health (NIOSH) conducted numerous air surveys to determine beryllium concentrations in various facilities. No detectable concentrations of beryllium were found in areas where machining of beryllium metal and alloys involved drilling, boring, cutting, and sanding (Gilles 1976; Bioana 1980; Lewis 1980, all cited in IARC 1993). During welding, air contamination depended on the type of welding process used and the concentration of beryllium in the compound being welded. The highest beryllium air emissions occurred in argon-arc welding (Bobrischev-Pushkin *et al.* 1975, cited in WHO 1990).

Kreiss *et al*. (1996) examined beryllium exposure measurements in a beryllia ceramics plant. Her group found that the daily weighted average (DWA) for machining processes exceeded that for any other occupation. Quarterly DWAs were estimated by a formula that incorporated average general area, full-shift area, and breathing zone measurements of beryllium. Table 2-8 summarizes these findings.

Table 2-8. Median of quarterly daily weighted averages (DWA) for a beryllia ceramics plant

Job	Dates of jobs	Median DWA ($\mu g/m^3$)	Number of DWA > 2.0 $\mu g/m^3$	Range ($\mu g/m^3$)
Jobs with DWAs over 2.0 $\mu g/m^3$				
Sawer/grinder	10/85 – 3/88	0.9	2	0.4 – 6.8
Lapper	4/88 – 3/92	0.6	2	0.2 – 2.1
Centerless grinder	4/88 – 3/92	0.5	1	0.1 – 8.2
Driller	4/88 – 3/92	0.3	2	0.1 – 4.9
Kiln operator	10/85 – 3/92	0.3	1	0.1 – 14.4
Dicer	4/88 – 3/92	0.1	1	0.1 – 2.2
Jobs with no DWAs over 2.0 $\mu g/m^3$				
Press setup operator	–	0.4	0	0.1 – 1.9
Janitor	–	0.3	0	0.1 – 1.0
Surface grinder	–	0.3	0	0.1 – 1.7
Material preparer	–	0.2	0	0.1 – 1.2
Green machinist	–	0.2	0	< 0.1 – 0.6
Tape operator	–	0.2	0	0.1 – 1.2
Small presser	–	0.1	0	< 0.1 – 0.8
Large presser	–	0.1	0	< 0.1 – 0.6
Isopresser	–	0.1	0	< 0.1 – 0.7
Engineering technician	–	0.1	0	< 0.1 - 0.6
Inspector	–	0.1	0	< 0.1 – 1.9
Front office employee	–	0.1	0	< 0.1 – 0.3
Metallizer	–	< 0.1	0	< 0.1 – 0.1

Source: Kreiss *et al.* (1996).

The median or quarterly DWA for machining processes was 0.9 $\mu g/m^3$, accounting for the majority of quarterly DWAs higher than the OSHA standard of 2.0 $\mu g/m^3$. Kreiss *et al.* (1996) calculated that 8.1% of the machining DWAs were above this OSHA standard.

2.7.3 Other occupational exposure scenarios

Dental laboratory technicians were found to be exposed to beryllium while processing beryllium-containing dental alloys. Dvivedi and Shen (1983, cited in WHO 1990) found that when exhaust extraction was used, beryllium exposure levels averaged 1.75 $\mu g/m^3$. Without exhaust extraction, however, beryllium exposure levels were as high as 74.3 $\mu g/m^3$.

OSHA also identified workers who grind, polish, and finish golf clubs containing a certain beryllium-copper alloy as occupationally exposed to beryllium. The average beryllium breathing-zone concentration of beryllium for these workers ranged from 2 to 14 μg/m^3 (OSHA, personal communication 1989, cited in WHO 1990).

2.8 Biological indices of exposure

Beryllium concentrations can be analyzed by various methods to determine exposure and body burden. While urine analysis may provide evidence of current exposure to beryllium compounds, analysis of blood, serum, or plasma can indicate the level of current exposure (Tsalev and Zaprianov 1984, cited in ATSDR 1993). Measured concentrations of beryllium in bodily fluids have decreased since 1983 probably as a result of better analytical techniques and more efficient ways of limiting beryllium contamination during collection and assay. Urine concentrations from non-occupationally exposed humans, identified by graphite furnace atomic absorption (GFAA), appear to have decreased, from 0.9 $\pm$ 0.4 μg/L (Grewal and Kearns 1977, cited in IARC 1993) to 0.13 μg/L (Paschal and Bailey 1986, cited in IARC 1993). Smoking appears to increase beryllium concentrations in urine. Apostoli *et al.* (1989, cited in IARC 1993) found that heavy smokers have beryllium urine levels (0.31 $\pm$ 0.17 μg/L) significantly higher than those of nonsmokers (0.20 $\pm$ 0.14 μg/L).

In a survey of 66 patients with chronic beryllium disease in the U.S. Beryllium Case Registry, beryllium concentrations ranged from 4 to 45,700 μg/kg dry lung tissue. Of the 66 patients, 82% had beryllium concentrations of more than 20 μg/kg dry weight. Beryllium levels ranging from 2 to 30 μg/kg dry lung tissue were found in 125 lung specimens from these patients during thoracic surgery (Sprince *et al.* 1976, cited in IARC 1993).

An exposure concentration of 2 μg/m^3 of beryllium in the air was found to correspond to beryllium concentrations in human urine and blood of about 7 μg/L and 4 μg/L, respectively. (Zorn *et al.* 1988, cited in IARC 1993).

Beryllium remains in major tissues for long periods, especially the bones and lymph nodes. Elimination of beryllium from the body can take months or years. Table 2-9 summarizes beryllium body burdens (HSDB 1997).

Table 2-9. Beryllium body burdens

Body site	Beryllium Concentration (µg/kg)
Total body burden	36
Soft tissue	24
Kidney	0.2
Liver	1.6
Muscle	0.75
Bone	3.0
Hair	6.0 - 20.0
Blood	0.02 - 3.0[a]
Urine	0.02 - 3.0[a]

Source: HSBD (1997)
[a] µg/L

2.9 Regulations

In 1980, the Consumer Product Safety Commission (CPSC) preliminarily determined that beryllium, beryllium oxide, and beryllium sulfate were not present in consumer products under its jurisdiction. Subsequently, public comment was solicited to verify the accuracy of this information; no comments were received. Pending receipt of new information, the CPSC plans no action on this chemical. In 1973, EPA promulgated a National Emissions Standard for Hazardous Air Pollutants (NESHAP) for extraction and production sites for beryllium and beryllium oxide and for beryllium rocket-motor firing. In 1980, EPA published a water quality criteria document on beryllium for the protection of human health under the Clean Water Act (CWA) and established regulations under the Resource Conservation and Recovery Act (RCRA) and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) for releases of beryllium and beryllium compounds. These regulations were based on the inclusion of beryllium and its compounds on the EPA Carcinogen Assessment Group's list of potential carcinogens. The CERCLA final reportable quantity (RQ) is 10 lb for beryllium and beryllium dust and 1 lb for beryllium chloride and beryllium fluoride. RCRA mandates that wastes known to contain beryllium or beryllium compounds comply with handling and report/recordkeeping requirements. EPA does not plan to regulate beryllium in drinking water under the Safe Drinking Water Act. Beryllium and its compounds are also regulated under the Superfund Amendments and Reauthorization Act (SARA), which subjects them to reporting requirements. U.S. EPA regulations are summarized in Table 2-10.

FDA regulates beryllium in bottled water under the Federal Food, Drug and Cosmetics Act (FD&CA) (see Table 2-11).

The American Conference of Governmental Industrial Hygienists (ACGIH) has classified beryllium as A1, “a confirmed human carcinogen” (ACGIH 1992). NIOSH considers beryllium an occupational carcinogen. NIOSH recommended that exposure to beryllium and beryllium compounds should not exceed 0.5 µg/m^3 (NIOSH 1992). Current OSHA standards for workers exposed to beryllium are: 2 µg/m^3 eight-hr TWA, 5 µg/m^3 ceiling,

and 25 μg/m^3 maximum peak in 30 minutes (see Table 2-12). These standards were adopted by OSHA for toxic effects other than cancer. OSHA has proposed regulating occupational exposure to beryllium, based on its carcinogenicity as well as other toxic effects. OSHA regulates beryllium and certain beryllium compounds under the Hazard Communication Standard and as chemical hazards in laboratories.

Table 2-10. U.S. EPA regulations

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 51.160ff. – SUBPART I – Review of New Sources and Modifications. Promulgated: 51 FR 40669, 11/07/86. U.S. Codes: 101(b)(1), 110, 160-169, 171-178, and 301(a), 42 U.S.C. 7401(b)(1), 7410, 7470-7479, 7501-7508, and 7601(a)); sec. 129(a).	In accordance with the policy of section 101(b)(1) of the act and the purposes of section 160 of the Act, each applicable State implementation plan shall contain emission limitations and such other measures as may be necessary to prevent significant deterioration of air quality. Beryllium emissions must not exceed 0.0004 tons per year.
40 CFR 61 – PART 61 – NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Codes: 7401, 7412, 7414, 7416, 7601.	This part lists substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants, and applies to the owner or operator of any stationary source for which a standard is prescribed under this part.
40 CFR 61.01 ff. – Subpart A – Lists of pollutants and applicability of part 61. Promulgated: 59 FR 12429, 03/16/94. U.S. Code: 42 U.S.C. 7661.	Substances that, pursuant to section 112 of the CAA, have been designated as hazardous air pollutants. Substances for which a Federal Register notice has been published that included consideration of the serious health effects from ambient air exposure.
40 CFR 61.30 ff. – Subpart C – National Emission Standard for beryllium. Promulgated: 38 FR 8826, 04/06/73. U.S. Code: 7401, 7412, 7414, 7416, 7601. Emissions to the atmosphere from stationary sources subject to the provisions of this subpart shall not exceed 10 grams of beryllium over a 24-hr period (see paragraph [b] of 40 CFR 61.32 for exception to the rule).	The provisions of 40 CFR 61.30 are applicable to machine shops that process beryllium, beryllium oxides, or any alloy containing more than 5 wt. % beryllium, ceramic plants, incinerators, propellant plants that process beryllium ore, alloys, and waste.
40 CFR 61.41 ff. – Subpart D – National Emission Standard for beryllium Rocket Motor Firing. Promulgated: 50 FR 46294, 11/07/85.	The provisions of this subpart are applicable to rocket motor test sites. Emissions to the atmosphere from rocket-motor test sites shall not cause time-weighted atmospheric concentrations of beryllium to exceed 75 μg-min/m^3 of air within the limits of 10 to 60 minutes, accumulated during any 2 consecutive weeks, in any area in which an effect adverse to public health could occur. If combustion products from the firing of beryllium propellant are collected in a closed tank, emissions from such tank shall not exceed 2 g/h and a maximum of 10 grams per day.

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 63 – PART 63 – NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Codes: 7401 et seq.; CAA.	Standards that regulate specific categories of stationary sources that emit (or have potential to emit) one or more hazardous air pollutants are listed in this part pursuant to section 112(b) of the CAA.
40 CFR 63.70 – Subpart D – Regulations Governing Compliance Extensions for Early Reductions of Hazardous Air Pollutants. Promulgated: 59 FR 53110, 10/21/94.	The provisions of this subpart apply to an owner/operator of an existing source wishing to obtain a compliance extension from a standard issued under section 112(d) of the CAA. Beryllium is listed as a high-risk pollutant with a weighting factor of 10.
40 CFR 63.800ff. – Subpart JJ – National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/07/95.	The provisions of this subpart apply to each facility that is engaged in the manufacture of wood furniture or wood furniture components and that is a major source as defined in 40 CFR 63.2. Beryllium salts and beryllium compounds are prohibited from use in cleaning and wash-off solvents.
40 CFR 116 – PART 116 – DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/1978. U.S. Codes: 33 U.S.C. 1251 et seq.	This regulation designates hazardous substances under section 311(b)(2)(a) of the FWPCA. The regulation applies to discharge of the substances identified in table 116.4 to surface waters. Beryllium fluoride, chloride, and nitrate were classified in this section as hazardous substances.
40 CFR 117 – PART 117 – DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. Promulgated: 44 FR 50776, 08/29/79. U.S. Codes: FWPCA 311(b)(2)(A) and 501(a).	Discharges to water of amounts equal to or greater than the RQ must be reported to U.S. EPA. Reportable quantity (RQ) for environmental releases to water is 1 lb (0.454kg) for Beryllium fluoride, chloride, and nitrate.
40 CFR 122 – PART 122 – U.S. EPA ADMINISTERED PERMIT PROGRAMS: THE NATIONAL POLLUTANT DISCHARGE ELIMINATION SYSTEM. Promulgated: 48 FR 14153, 04/01/83. U.S. Code: 33 U.S.C. 1251 et seq., CWA.	Regulations cover basic U.S. EPA permitting requirements for effluent discharges from point sources to waters of the United States. Appendix D lists pollutants that must be identified by dischargers if expected to be present.
40 CFR 141 – PART 141 – NATIONAL PRIMARY DRINKING WATER REGULATIONS. Promulgated: 40 FR 59570, 12/24/75. U.S. Codes: U.S.C. 300.	To protect a safe drinking water supply, community and non-transient, non-community water systems must monitor for certain compounds listed.
40 CFR 141.21 ff. – SUBPART C – Monitoring and Analytical Requirements. Promulgated: 60 FR 34085, 06/29/95.	States that Atomic absorption (platform and furnace) and Inductively coupled plasma (along with mass spectrometry) should be used to analyze Beryllium levels in drinking water. Detection limits and RCLs are given.

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 141.31 ff. – Subpart D – Reporting, Public Notification and Record keeping. Promulgated: 59 FR 53110, 10/21/94.	A supplier of water shall report to the State the results of any test measurement or analysis required by this part. This part gives background information on several compounds with health concerns at certain levels of exposure. U.S. EPA has set the drinking water standard for beryllium at 0.004 ppm to protect against the risk of these adverse health effects.
40 CFR 141.50 ff. – Subpart F – Maximum Contaminant Level Goals. Promulgated: 50 FR 46901, 11/13/85.	The MCLG for beryllium in primary drinking water is 0.004 mg/L.
40 CFR 141.60 ff. – Subpart G – National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels. Promulgated: 60 FR 33932, 06/29/95.	Revised maximum contaminant levels for beryllium in drinking water is 0.004 mg/L.
40 CFR 142 – PART 142 – NATIONAL PRIMARY DRINKING WATER REGULATIONS IMPLEMENTATION. Promulgated: 41 FR 2918, 01/20/1976. U.S. Code: 42 U.S.C. 300g, 300g-1, 300g-2, 300g-3, 300g-4, 300g-5, 300g-6, 300j-4, and 300j-9;	This part sets forth regulations for the implementation and enforcement of the national primary drinking water regulations contained in part 141 of this chapter.
40 CFR 172 – SUBPART B – Table of Hazardous Materials and Special Provisions. Promulgated: 61 FR 50623, 50624, 09/26/96. The reportable quantity for beryllium, beryllium chloride and beryllium compounds is 10 lb (4.54 kg). The reportable quantity for beryllium fluoride and beryllium nitrate is 1 lb (0.454 kg).	The Hazardous Materials Table in this section designates beryllium and beryllium compounds as hazardous materials for the purpose of transportation of those materials. beryllium's identification number is UN 1567; beryllium nitrate is UN 2464, and beryllium compounds is UN 1567.
40 CFR 192 – PART 192 – HEALTH AND ENVIRONMENTAL PROTECTION STANDARDS FOR URANIUM AND THORIUM MILL TAILINGS. Promulgated: 48 FR 602, 01/05/1983. U.S. Codes: 42 U.S.C. 2022, as added by the Uranium Mill Tailings Radiation Control Act of 1978. Appendix 1 lists beryllium and beryllium compounds as constituents that need to be monitored.	The provisions of this part control the residual radioactive material at designated processing or depository sites under section 108 of the Uranium Mill Tailings Radiation Control Act of 1978, and applies to the restoration of such sites following any use of the subsurface minerals under section 104(h) of the Uranium Mill Tailings Radiation Control Act of 1978.
40CFR192.40 ff. – Subpart E – Standards for Management of Thorium Byproduct Materials Pursuant to Section 84 of the Atomic Energy Act of 1954, as Amended. Promulgated: 48 FR 45947, 10/07/83.	RCRA Appendix VIII hazardous waste constituents are regulated by reference in this part.
40 CFR 228 – PART 228 – CRITERIA FOR THE MANAGEMENT OF DISPOSAL SITES FOR OCEAN DUMPING. Promulgated: 42 FR 2482, 01/11/1977. U.S. Codes: 33 U.S.C. 1412 and 1418.	The criteria of this part apply to the evaluation of proposed ocean dumping under Title I of the Act, and effective management of ocean disposal sites to prevent unreasonable degradation of the marine environment from all wastes being dumped in the ocean.

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 258 – PART 258 – CRITERIA FOR MUNICIPAL SOLID WASTE LANDFILLS. Promulgated: 56 FR 51016, 10/09/91. U.S. Codes: 33 U.S.C. 1345(d) and (e); 42 U.S.C. 6907(a)(3), 6912(a), 6944(a) and 6949a(c).	The provisions of this part establish minimum national criteria under RCRA, as amended, for all MSWLF units and under the CWA, as amended, for MSWLF that are used to dispose of sewage sludge. The criteria ensure the protection of human health and the environment. Suggested methods of detecting beryllium and beryllium compounds in sewage sludge are U.S. EPA methods 6010 (PQL = 3 mg/L), 7090 (PQL = 50 mg/L), and 7091 (PQL = 2 mg/L).
40 CFR 261 – PART 261 - IDENTIFICATION AND LISTING OF HAZARDOUS WASTE. Promulgated: 45 FR 33119, 05/19/80. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6921, 6922, 6924(y) and 6938.	This part identifies those solid wastes which are subject to regulation as hazardous wastes under parts 262 through 265, 268, and parts 270, 271, and 124 of this chapter and which are subject to the notification requirements of section 3010 of RCRA. General exclusion levels for K061, K062, and F006 non-wastewater HTMR residues for beryllium is 0.010 mg/L.
40 CFR 261.30ff. – Subpart D – Lists of Hazardous Wastes. Promulgated: 55 FR 11863, 03/29/90.	The U.S. EPA Hazardous waste number for beryllium powder is P015.
40 CFR 264 – PART 264 – STANDARDS FOR OWNERS AND OPERATORS OF HAZARDOUS WASTE TREATMENT, STORAGE, AND DISPOSAL FACILITIES. Promulgated: 45 FR 33221, 05/19/80. U.S. Codes: 42 U.S.C. 6905, 6912(a), 6924, and 6925.	The purpose of this part is to establish minimum national standards that define the acceptable management of hazardous waste. The standards in this part apply to owners and operators of all facilities which treat, store, or dispose of hazardous waste, except as specifically provided otherwise in this part or part 261 of this chapter.
40 CFR 264.1200ff. – SUBPART EE – Hazardous Waste Munitions and Explosives Storage. Promulgated: 62 FR 6652, 02/12/97.	The requirements of this subpart apply to owners or operators, who store munitions and explosive hazardous wastes, except as §264.1 provides otherwise. The suggested method of detecting beryllium in groundwater is U.S. EPA method 6010 (PQL = 3 mg/L).
40 CFR 265.1200 ff. – SUBPART EE – Hazardous Waste Munitions and Explosives Storage. Promulgated: 62 FR 6653, 01/12/97.	The purpose of this subpart is to outline design and operating standards where munitions and explosive hazardous waste, including compounds containing beryllium and beryllium compounds, are stored.
40 CFR 266.100 ff. – Subpart H – Hazardous Waste Burned in Boilers and Industrial Furnaces. Promulgated: 56 FR 7208, 02/21/91.	Appendix V of Part 266 lists a risk specific dose of 4.2×10^{-3} $\mu g/m^3$ for beryllium.
40 CFR 268 – PART 268 – LAND DISPOSAL RESTRICTIONS. Promulgated: 62 FR 26019, 05/12/ 97. U. S. Codes: 42 U.S.C. 6905, 6912(a), 6921, and 6924.	This part identifies hazardous wastes that are restricted from land disposal and defines those limited circumstances under which an otherwise prohibited waste may continue to be land disposed.

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 268.40ff. – SUBPART D – Treatment Standards. Promulgated: 62 FR 32979, 06/17/97.	Prohibited waste identified in the table "Treatment Standards for Hazardous Wastes" may be land disposed only if it meets the requirements found in the table. Water disposal requires that it meat certain hazardous waste concentration requirements. beryllium wastewater standard is 0.082 mg/L while the non-wastewater standard is 0.014 mg/L.
40 CFR 302 – Part 302 – Designation, Reportable Quantities, And Notification. Promulgated: 50 FR 13474, 04/04/85. U.S. Codes: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361. beryllium and beryllium compounds have a regulatory RQ of 1lb (0.454 kg) which was set by CERCLA. No final RQ was set because this is a broad category of compounds.	This part designates under section 102(a) of CERCLA 1980 those substances in the statutes referred to in section 101(14) of CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This part also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.
40 CFR 372 – PART 372 – TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Codes: 42 U.S.C. 11013, 11028. Effective date for beryllium is 1/1/87.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA (1986). Information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, to aid in the development of regulations, guidelines, and standards.
40 CFR 401 – PART 401 – GENERAL PROVISIONS. Promulgated: 47 FR 24537, 06/04/82. U.S. Codes: 33 U.S.C. 1251 et seq.	The provisions of this part set forth the legal authority and general definitions which will apply to all regulations issued concerning specific classes and categories of point sources of industrial effluents under parts 402 through 699. In this section beryllium and beryllium compounds are identified as a toxic pollutant by the Federal Water Pollution Control Act.
40 CFR 403 – PART 403 – GENERAL PRETREATMENT REGULATIONS FOR EXISTING AND NEW SOURCES OF POLLUTION. Promulgated: 46 FR 9439, 01/28/81. U.S. Codes: Several sections of the FWPCA and the CWA of 1977 (Public Law 95-217).	Establishes responsibilities of federal, state, and local government; industry; and the public to implement National Pretreatment Standards to control pollutants that pass through POTWs and contaminate sewage sludge or interfere with treatment processes.
40 CFR 403.18 – Sec. 403.18 Modification of POTW Pretreatment Programs. Promulgated: 53 FR 40615, 10/17/88	Appendices list 65 Toxic Pollutants, including beryllium, (51 FR 20431, 06/04/86) and industrial categories subject to National Categorical Pretreatment Standards (51 FR 20429, 06/04/86).
40 CFR 421 – PART 421 – NONFERROUS METALS MANUFACTURING POINT SOURCE CATEGORY. Promulgated: 49 FR 8790, 03/08/84. U.S. Codes: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), 1318, and 1361.	The provisions of this part apply to facilities producing primary metals from ore concentrates and recovering secondary metals from recycle wastes which discharge pollutants to waters of the U.S. or which introduce or may introduce pollutants into a POTW.

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 421.150 ff. – SUBPART O - Primary beryllium Subcategory. Promulgated: 50 FR 38346, 09/20/85.	The provisions of this subpart are applicable to discharges resulting from the production of beryllium by primary beryllium facilities processing beryllium ore concentrates or beryllium hydroxide raw materials. Effluent limitations are given in the subsequent sections.
40 CFR 423 – PART 423 – STEAM ELECTRIC POWER GENERATING POINT SOURCE CATEGORY. Promulgated: 47 FR 52304, 11/19/82. U.S. Codes: 33 U.S.C. 1311; 1314(b), (c), (e), and (g); 1316(b) and (c); 1317 (b) and (c); and 1361.	The provisions of this part apply to discharges resulting from the operation of a generating unit by an establishment generating electricity for distribution and sale which results from a process utilizing fossil-type or nuclear fuel in conjunction with a thermal cycle that uses the steam water system as the thermodynamic medium.
40 CFR 468 – PART 468 – COPPER FORMING POINT SOURCE CATEGORY. Promulgated: 48 FR 36957,08/15/83. U.S. Code: 33 U.S.C. 1311, 1314(b), (c), (e), and (g), 1316(b) and (c), 1317(b) and (c), and 1361.	The provisions of this part apply to discharges resulting from the manufacture of formed copper and copper alloy products.

Source: The regulations in this table have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1996; 21 CFR, April 1, 1996; 29 CFR, July 1, 1996

Table 2-11. FDA regulations

FDA Regulations	
Regulatory action	Effect of regulation and other comments
21CFR165-- PART 165--BEVERAGES. Promulgated: 60 FR 57124, 11/13/95 effective 5/13/96. U.S. Code: 21 U.S.C. 321, 341, 343, 343A, 348, 349, 371, 379e.	The regulations in subparts A and B govern the labeling and effective chemical substance limits for specific standardized beverages.
21CFR165.110 ff-- Subpart B--Requirements for Specific Standardized Beverages-- Bottled water: Allowable concentration of beryllium in bottled water is 0.004 mg/L. The levels for beryllium are stayed until further notice.	Allowable concentrations for inorganic substances, volatile organic chemicals (VOCs) and other chemical substances are given in this subpart.

Source: The regulations in this table have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1996; 21 CFR, April 1, 1996; 29 CFR, July 1, 1996

Table 2-12. OSHA regulations for beryllium and beryllium compounds

OSHA Regulations	
Regulatory action	Effect of regulation and other comments
29 CFR 1910.1000—Sec. 1910.1000 Air Contaminants. Promulgated: 58 FR 40191, 07/27/93. OSH Act: Air Contaminants.	As beryllium, PEL 2 µg/m^3 8-hr TWA; 5 µg/m^3 ceiling; 25 µg/m^3 maximum peak for 30 min.
29 CFR 1910.1200, 1915, 1917, 1918, 1926, 1928. Promulgated: 61 FR 9245, 03/07/96. OSH Act: Hazard Communication.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, material safety data sheets, and worker training.
29 CFR 1910.1450—Sec. 1910.1450 Occupational Exposure to Hazardous Chemicals in Laboratories. Promulgated: 61 FR 5508, 02/13/96. OSH Act: Final rule for occupational exposure to hazardous chemicals in laboratories.	As select carcinogens (IARC Group 2A), beryllium and certain beryllium compounds are included as chemical hazards in laboratories. Employers are required to provide employee information and training and a Chemical Hygiene Plan.
29 CFR 1926.55(a)—Sec. 1926.55 Safety and Health Regulations for Construction. Promulgated: 39 FR 22801, 07/24/74. OSH Act: Final Standard (Construction Industry).	PEL 2 µg/m^3 8-hr TWA.

Source: The regulations in this table have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1996; 21 CFR, April 1, 1996; 29 CFR, July 1, 1996

3 Human Cancer Studies

Beryllium and beryllium compounds were classified as carcinogenic to humans when evaluated by IARC (1993). Since the IARC review, three new epidemiologic studies of cancer among beryllium-exposed workers (Rooney *et al.* 1993; Wing *et al*. 1993; Loomis and Wolf 1996) and one study describing an autopsy case-series of workers with chronic beryllium disease (Williams 1996) have been published. The quality of the epidemiologic evidence concerning beryllium has improved in the last decade. Nevertheless, the absence of quantitative information on exposures to beryllium remains an important limitation of the current literature. Four other reviews of epidemiologic studies, relevant to the carcinogenicity of beryllium, were also published after the IARC evaluation (Boffetta 1993; MacMahon 1994; Steenland *et al*. 1996; Hayes 1997). Most support the conclusions of the 1993 IARC monograph (Boffetta 1993; Steenland *et al.* 1996; Hayes 1997), but MacMahon (1994) criticized the conclusion that beryllium is carcinogenic, citing cigarette smoking as an alternative explanation. Interpretations of recent evidence on beryllium have also been offered in editorials and published letters (Saracci 1991; Eisenbud 1993; Steenland and Ward 1991; BISAC 1997; Vainio and Rice 1997).

This section summarizes the content and conclusions of the IARC Working Group's 1993 evaluation of beryllium and presents key findings of relevant epidemiologic studies published since that review.

3.1 IARC Evaluations

Human studies on the carcinogenicity of beryllium and beryllium compounds have been reviewed by four IARC Working Groups (IARC 1972, 1980, 1987, and 1993). The 1980 Working Group characterized the human evidence of carcinogenicity available at that time as limited. No new human studies were available when beryllium was next evaluated in 1987. The 1993 evaluation incorporated two cohort studies and a nested case-control study published since the previous review. After taking this new evidence into account, the Working Group classified beryllium and beryllium compounds as human carcinogens, based on sufficient evidence in epidemiologic studies of exposed workers.

The IARC Working Group summarized the human evidence of carcinogenicity in 1993 (IARC 1993). Early retrospective cohort mortality studies showed a consistent excess of deaths from lung cancer (Mancuso 1979; Mancuso 1980; Wagoner *et al*. 1980; all cited in IARC 1993).

The first study followed mortality through 1975 among a cohort of white men employed at two beryllium extraction, production, and fabrication facilities in the United States between 1942 and 1948. The standardized mortality ratio (SMR) for lung cancer was 1.8 (95% CI 1.2 - 2.7) among 1,222 men employed in one plant and 1.25 (95% CI 0.9 - 1.7) for 2,044 men in the other plant. The combined SMR for lung cancer in the two plants was 1.42 (95% CI 1.1 - 1.8) (Mancuso 1979; cited in IARC 1993). The excess of lung cancer was greatest for men employed during the period when exposures were highest,

before 1949, and increased with time since exposure: workers followed at least 15 years had lung cancer SMRs of 2.0 (95% CI 1.3 - 3.1) and 1.5 (95% CI 1.0 - 2.1) in the two plants. The SMRs cited in the IARC Working Group incorporate an adjustment for the lack of national mortality data for the years 1965-67. This study did not include analyses of mortality by job title or exposure category.

A subsequent re-analysis of mortality in the two plants by the same author expanded the period of employment to 1937-48, and used a cohort of viscose rayon workers, rather than the general population, as a referent group (Mancuso 1980; cited in IARC 1993). The SMR for lung cancer among the 3,685 workers in both plants was 1.40 ($P < 0.01$). The SMR for lung cancer was highest among men employed the longest in the beryllium plants, but did not increase steadily with duration of employment among men with shorter tenure: the lung cancer SMR was 1.38 (n = 52; $P < 0.05$) for $\leq$1 year, 1.06 (n = 14) for 1- 4 years, and 2.22 (n = 14; $P < 0.01$) for > 4 years (Mancuso 1980; cited in IARC 1993).

Wagoner *et al.* (1980; cited in IARC 1993) conducted an expanded study of mortality among workers at one of the two plants studied previously (Mancuso 1979, 1980), including men employed 1942-1967. Among the 3,055 workers, the SMR for lung cancer was 1.25 (95% CI 0.9 - 1.7). The Working Group noted that the average exposure in this cohort may have been lower than in previous studies because the study period extends across the year 1949, when levels of beryllium in workplaces were reduced markedly by a new exposure limit. The risk of lung cancer increased with latency, from 0.88 among workers with < 15 years latency, to 1.16 for 15 - 24 years' latency, and 1.68 (95% CI 1.0 - 2.6) for ≥ 25 years' latency. The investigators attempted to assess potential confounding by smoking using indirect adjustments. The IARC Working Group noted that these adjustments suggested the possibility of bias in opposite directions: estimates of smoking prevalence from a survey of a portion of the cohort suggested that smoking practices could have increased the workers' risk of lung cancer by 14% in the absence of any effect of beryllium, while local lung cancer rates suggested that the use of national rates in the analysis may have underestimated the risk by 19% (Wagoner *et al.* 1980; cited in IARC 1993).

Infante *et al.* (1980, cited in IARC 1993) analyzed the mortality of white men enrolled in a beryllium case registry with a diagnosis of chronic beryllium disease or acute beryllium-induced pneumonitis. The registry was established in 1952 to characterize the epidemiology and clinical features of beryllium -related diseases, and the participants had been employed in a variety of industries, primarily beryllium extraction and smelting, metal production, and fluorescent tube production. Among 421 white males enrolled between 1952 and 1975, there were 7 deaths from lung cancer, yielding an SMR of 2.12, based on 1952 to 67 national mortality rates. The Working Group estimated that adjustment for the gap in U.S. mortality data between 1968 and 1975 would alter the SMR to 1.93 (95% CI 0.8 - 4.0). Most of the lung cancer deaths (6 cases) occurred among men enrolled with a diagnosis of acute beryllium-induced pneumonitis; the corrected SMR for this group was 2.98 (95% CI 1.0 - 6.2). The Working Group noted

that exposures were likely to have been higher among workers with beryllium-related acute pneumonitis than among men with chronic beryllium disease (IARC 1993).

The 1993 IARC evaluation also included two later cohort studies. Ward *et al.* (1992) followed the mortality through 1988 of 9,225 male workers (8,905 white, 320 non-white) employed as early as 1935 at seven beryllium plants in the U.S.A., including the two studied previously. Mortality from all causes and all cancers was essentially as expected, while the SMR for lung cancer was 1.26 (95% CI 1.12 - 1.42) and for non-malignant respiratory disease the SMR was 1.48 (1.21 - 1.80). Lung cancer mortality increased with time since exposure (latency), but not with duration of employment. Although lung cancer mortality was highest in the oldest plant and in the 1940s, when exposures were highest, excess lung cancer was also observed in other plants and for workers hired in the 1940s. Mortality from cancers at sites other than the lung was not increased. The investigators performed adjustments based on the use of local, rather than national, death rates and on partial data on smoking in the cohort and concluded that neither could account for the excess risk of lung cancer (Ward *et al*. 1992).

Steenland and Ward (1991) expanded the analysis of mortality in the previously studied U.S. Beryllium Case Registry to include 689 women and men of all races enrolled 1952 to 1980 and extended the follow-up of mortality through 1988. The SMR for lung cancer was 2.00 (n = 28, 95% CI 1.33 - 2.89). This excess was greater in those who were entered into the Registry with acute beryllium pneumonitis (SMR 2.32, 95% CI 1.35 - 3.72). The prevalence of smoking among cohort members surveyed in 1965 was lower than average for the U.S. population, so the authors concluded that smoking was unlikely to explain the increased risk for lung cancer (Steenland and Ward 1991).

Two case-control studies were included in the IARC (1993) review. Hinds *et al.* (1985) used a computerized job-exposure matrix to assess occupational exposures in a population-based study of incident lung cancer in Hawaii. Between 1979 and 1982, 261 new cases of primary lung cancer were diagnosed among males (race not given). Lung cancer was associated with occupational exposure to beryllium (OR 1.62, 95% CI 1.04 - 2.51 and 1.57, 95% CI 0.81 - 3.01 for low and high beryllium exposures, respectively, relative to no exposure).

Carpenter *et al.* (1988) conducted a nested case-control study of 89 men and women with cancer of the central nervous system, each matched to four controls, among workers at two nuclear facilities at Oak Ridge, Tennessee. Exposures to 26 chemicals, including beryllium were assessed by job title and expert judgement. The odds ratio for “ever having been exposed to beryllium” was 1.5 (95% CI 0.6 - 3.9). The strength of the association increased with both presumed exposure level and latency, but the precision of the estimated ORs was limited.

The IARC Working Group emphasized several aspects of the most recent cohort studies in order to justify their conclusion that the environment of workers producing, refining and machining beryllium and beryllium alloys is causally related to lung cancer: 1) the statistical stability of the association; the consistency of the association across several

plants and populations; 2) the greater risk among workers hired before exposure controls were introduced; 3) the increasing risk with longer latency; 4) the increased risk in plants where the risk of beryllium-related non-malignant respiratory disease was highest, and 5) the increased risk among members of the Beryllium Case Registry with beryllium-related lung disease.

Key limitations of these studies noted by the Working Group are the absence of quantitative, individual measurements of exposure to beryllium and other occupational agents and the relatively low excess risk of lung cancer.

3.2 Current epidemiologic studies

Two case-control studies and two cohort studies published since the IARC review provide some additional information about the carcinogenicity of beryllium.

3.3 Case-control studies

Rooney *et al.* (1993) conducted a case-control study of prostate cancer incidence and mortality in 1946-86 among men employed by the United Kingdom Atomic Energy Authority (UKAEA). In this study, 136 men with prostate cancer were matched to 404 control men by age and calendar year of first employment, survival time, last place of employment, and monitoring for internal exposure to radionuclides. Individual information about social and demographic characteristics, work history, and internal exposures to radionuclides was abstracted from UKAEA records. Exposures to specific radionuclides and other potential hazards, including beryllium, were assessed by expert judgement based on work areas. A history of work in locations where beryllium was potentially present was found in 5% of the cases and 6% of the controls, yielding an odds ratio of 0.87 (95% CI 0.03 - 2.17)

The Children's Cancer Group (Buckley *et al.* 1998) conducted a case-control study of environmental and familial factors in the etiology of Ewing's sarcoma and osteosarcoma in children based on parental exposure to beryllium. Patients were identified in the registration data of the Children's Cancer Group. The osteosarcoma patients selected were less than 18 years of age and were diagnosed between January 1, 1982 and December 31, 1983. Children with Ewing's sarcoma were younger than 21 years and diagnosed between January 1, 1983 and July 30, 1985. Interviews with parents were conducted between October 1983 and February 1987. The studies were conducted separately, hence the different accrual periods and age eligibilities. However, the design and study questionnaires for each study were kept similar to facilitate comparisons. The parents of 152 children with osteosarcoma and 153 children with Ewing's sarcoma were interviewed by telephone, with controls obtained by random digit dialing, and matched to cases by age and race. This study did not find any important risk factors for either type of childhood bone tumor. No occupational category or specific exposure was associated with the occurrence of bone tumors. Although beryllium was of interest, no clear associations between maternal or paternal occupational exposures and osteosarcoma in offspring could be identified. There was no difference between cases and controls for maternal or paternal exposures to metals, welding, soldering, or mining and

manufacturing. For maternal exposure to metals, the OR for osteosarcoma was 3.50 (P = 0.11), and for Ewing's sarcoma, 1.12 (P = 0.81). For paternal exposure to metals, the OR for osteosarcoma was 0.74 (P = 0.34), and for Ewing's sarcoma, 1.09 (P = 0.77) (Buckley *et al.* 1998).

3.4 Cohort studies

Two recent cohort studies of U.S. nuclear workers also included workers exposed to beryllium. Wing *et al.* (1993) evaluated the association of all cancer with job titles and exposures to beryllium, mercury, and lead among white men employed at Oak Ridge National Laboratory in the United States. The primary goal of the study was to gauge whether other occupational exposures could explain previously-reported associations of cancer with exposure to ionizing radiation among the cohort. No information on the level of non-radiation exposures was available, but 609 workers were known to have worked with beryllium. Mortality from all cancers combined was increased 38% among these workers, who were almost exclusively nonsmokers. No data were presented for lung cancer or other specific cancers in relation to beryllium exposure.

Loomis and Wolf (1996) analyzed mortality among men and women of all races employed at the Y-12 nuclear materials production plant from 1947 and 1974 and followed through 1990. The plant was one of those studied previously by Carpenter *et al.* (1988); beryllium was known to have been used, but no quantitative measurements of exposure were available. Lung cancer mortality was elevated among all workers at the plant (SMR 1.17, 95% CI 1.01 - 1.34) and among the white males (SMR 1.20, 95% CI 1.04 - 1.38). The risk was highest among workers hired from 1947 to 54 and among those with 10 to 29 years latency and 5 to 19 years of employment. Lung cancer mortality was quantitatively associated with cumulative radiation dose in a previous study of the plant.

3.5 Other studies

Williams (1996) reported on a case-series of 30 workers in the United Kingdom who had died from chronic beryllium disease. The majority of the workers were fluorescent lamp workers and machinists who died from respiratory failure. Autopsies were conducted on 19 of the workers: most showed interstitial pulmonary fibrosis with varying degrees of cystic change, but no lung cancers were found.

3.6 Discussion

The quality of the epidemiologic evidence on the carcinogenicity of beryllium has improved substantially in the last decade. Early studies suggested an association of lung cancer with exposure to beryllium, but were limited by small numbers, short follow-up intervals, problems in estimating expected numbers of deaths due to missing national mortality data, and lack of direct measurements of exposure to beryllium and potential confounders. These problems have been addressed in recent studies. The remaining weakness of these studies is the absence of quantitative information on individual exposure; this is as likely to attenuate as to inflate observed risks.

The two cohort studies published from 1987 to 1993 strengthen the evidence for carcinogenicity. The study by Ward *et al.* (1992) represents a particularly significant advance relative to earlier efforts, with substantial increases in sample size and follow-up time, a larger number of plants, and use of appropriate referent mortality rates in the analysis. As in earlier research, the absence of information on beryllium exposure remained a key limitation in this study. Nevertheless, the results are consistent internally and externally, and the patterns of risk are consistent with a causal association between beryllium and lung cancer risk.

The results of cohort studies published after the 1993 IARC review (Wing *et al*. 1993; Loomis and Wolf 1996) are consistent with earlier findings, but add relatively little new evidence specifically concerning beryllium. Both studies focused on nuclear workers in facilities where beryllium was used in conjunction with other chemicals and where exposures to ionizing radiation were documented. One of the studies (Wing *et al*. 1993) examined the mortality of a group of workers known to have worked with BE and found evidence of increased mortality from cancer among them. However, neither study included quantitative information on beryllium exposures, which would play an important part in efforts to separate the effects of beryllium from those of radiation and other agents.

The population in the case-control study by Rooney *et al.* (1993) likewise included nuclear workers with exposures to multiple chemicals and ionizing radiation. This study's assessment of exposure to beryllium by expert judgement represents an improvement relative to other studies with no information about exposure. However, the study considered only prostate cancer, which has not been associated with beryllium exposures in previous studies. The negative results of this study for beryllium are therefore consistent with expectations.

The case-series study of individuals with chronic beryllium disease reported by Williams (1996) differs in design from earlier follow-up studies of participants in a beryllium disease registry (Infante *et al*. 1980; Steenland and Ward 1991). No lung cancer was identified among the beryllium workers studied by Williams. However, the study did not include information about age and follow-up time, which would be needed to calculate mortality rates and expected numbers of deaths. Given the small size of the series (n = 30), the expected number of lung cancer cases may have been close to zero. In addition, the series was limited to workers with chronic beryllium disease, which was associated with lower rates of lung cancer in earlier studies, relative to acute beryllium disease.

Critiques of the recent epidemiologic literature on beryllium and cancer have cited the inability to control directly for cigarette smoking in any of the studies as a critical limitation (MacMahon 1994; BISAC 1997). Confounding by smoking is a potential threat to validity in any study of the role of occupational exposures in lung cancer, particularly when the magnitude of the association is modest. In the case of beryllium, however, no evidence has been presented to indicate that the prevalence of smoking in any of the exposed cohorts was substantially greater than in the referent population. In the absence

of such evidence, arguments that smoking is the most likely explanation for the observed associations (MacMahon 1994) are speculative.

Tobacco smoke may, however, be of concern as a potential modifier of the effect of beryllium. For some occupational lung carcinogens, notably asbestos and radon, the risk of cancer is markedly increased among exposed smokers. It is not currently possible to evaluate this relationship for beryllium because of the absence of individual information on beryllium exposure and smoking.

Exposure to sulfuric acid mists has also been proposed as an alternative explanation for excess lung cancer among beryllium workers (BISAC 1997). Sulfuric acid has been designated as a *human carcinogen* by IARC and was used in one beryllium plant that had a large influence on the results of studies by Mancuso (1979; 1980) and Ward *et al.* (1992). However, excess lung cancer was also observed in facilities that did not employ the sulfuric acid process used in that plant (Wagoner 1980; Ward *et al*. 1992). Moreover, the finding that lung cancer risk is significantly increased among workers with beryllium disease and that the risk appears to increase with the intensity of beryllium exposure supports a conclusion that beryllium is causally related to lung cancer risk. Finally, although exposure to sulfuric acid mists is associated with laryngeal cancer, the evidence supporting a relationship to lung cancer is weak (Sathiakumar *et al.* 1997).

Thus, the epidemiologic evidence as a whole supports a conclusion that beryllium is carcinogenic to humans. Although the reported increases in cancer risk are relatively modest, they have been observed consistently in most locations studied. Small increases in risk may result from dilution of an effect by poor specificity in classifying exposure. Existing studies of populations exposed to beryllium have used relatively crude exposure classifications, generally treating all workers in a plant as exposed, although some may have had no contact with beryllium. Risks may be larger among truly-exposed workers. This interpretation is supported by the risk of lung cancer among individuals with beryllium-related disease, whose exposure to beryllium is known. In general, cancer risks do not appear to increase with duration of employment in beryllium-processing facilities. However, the temporal patterns of risk observed in studies of beryllium worker cohorts and persons with beryllium-related lung disease suggest that excess lung cancer may have been associated with intense, short-term exposures, rather than with long-term, low-level exposures. Epidemiologic studies of workers exposed to beryllium also suggest that the risk of cancer increases with time since exposure to beryllium (latency), a pattern that is consistent with a causal role.

Table 3-1. Current case-control studies of cancer

Reference	Study Design	Population	Exposure	Effects	Potential Confounders
Rooney *et al.* (1993) United Kingdom	Case-control	136 men with prostate cancer diagnosed from 1946 to 1986 and 404 matched controls, all employees of United Kingdom Atomic Energy Authority.	Individual work history and radiation exposure were abstracted from Atomic Energy Authority records. Exposure to beryllium was assessed by expert judgement, according to work location. Exposure levels were ranked as: none or unlikely; probable but relatively low level, or probable and relatively high level. If probable, calendar years and frequency of exposure recorded.	Risk of prostate cancer associated with working in places assessed to be potentially contaminated with beryllium RR=0.87 (0.30 - 2.17), relative to never having worked in a place potentially contaminated with relevant substance or radiation.	Multiple exposures (15 specific radionuclides, 6 metals, 3 groups of chemicals, 3 physical agents, 7 other types of radiation).
Buckley *et al.* (1998) U.S.A.	Case-control	152 children with osteosarcoma and 153 children with Ewing's sarcoma. Patients were identified in the registration data of the Children's Cancer Group. Patients with osteosarcoma who were younger than 18 years and diagnosed from January 1, 1982 to December 31, 1983 were selected. Children with Ewing's sarcoma were younger than 21 years and diagnosed from January 1, 1983 to July 30, 1985.	Parents of cases were interviewed by telephone. Controls were obtained by random digit dialing and matched to cases by age and race.	OR and *P*-value for occupational exposure of parents of children with osteosarcoma and Ewing's sarcoma compared with controls. Maternal exposure to metals: OR = 3.50, *P* = 0.11 for osteosarcoma; OR = 1.12, *P* = 0.81 for Ewing's disease. Paternal exposure to metals: OR = 0.74, *P* = 0.34 for osteosarcoma; OR = 1.09, *P* = 0.77 for Ewing's disease.	Results not presented separately for beryllium; instead classification was exposure to metals.

Table 3-2. Current cohort studies of cancer

Reference	Study Design	Population	Exposure	Effects	Potential Confounders
Wing *et al.* (1993) U.S.A.	Historical cohort	8,318 white male workers employed at Oak Ridge National Laboratory,	609 workers known to have worked with beryllium.	All cancer RR 1.38 (95% CI 0.95 - 2.00)	Ionizing radiation, other metals.
Loomis and Wolf (1996) U.S.A.	Historical cohort	8,116 men and women of all races employed at the Y-12 nuclear materials plant, 1947 to 74 and followed to 1990	Beryllium known to have been used in the plant	Lung cancer SMR 1.17 (95% CI 1.01 - 1.34) for all workers and 1.19 (95% CI 1.03 - 1.36) for white males. Excess brain and lymphopoietic among white males.	Ionizing radiation, other metals, solvents, cutting fluids, no adjustment for cigarette smoking.

4 Studies of Cancer in Experimental Animals

4.1 Inhalation studies in rats, hamsters, rabbits, and monkeys

Groups of 60 and 33 male Charles River rats and 30 Greenacres Controlled Flora rats (more than four weeks old) were exposed by inhalation to metallic beryllium in the form of beryl ore (containing 4.14% beryllium, 63.6% crystalline silica, 18.1% Al_2O_3, and lower concentrations of other metal salts; mean particle diameter, 0.64 μm) or bertrandite ore (1.4% beryllium, 63.9% SiO_2, 9.8% Al_2O_3, and lower concentrations of other metals salts; mean particle diameter, 0.27 μm). Chamber concentration was 15 mg/m^3 of dust, and animals were exposed for six hours per day, five days a week for up to 17 months. The beryl ore atmosphere contained 620 μg/m^3 beryllium, and the bertrandite ore atmosphere contained 210 μg/m^3 of beryllium. A third group of rats served as controls and was housed in inhalation chambers without exposure. Of animals killed after 12 months of exposure, 5/11 exposed to beryl ore had foci of squamous metaplasia or small epidermoid tumors. After 17 months, 18/19 had lung tumors (18 bronchiolar alveolar-cell tumors, 7 adenomas, 9 adenocarcinomas, and 4 epidermoid tumors). Exposure to bertrandite ore caused pulmonary granulomatous lesions and some proliferative changes, but lung tumors were not observed. Interpretation of this study was confounded by the presence of crystalline silica in the beryl ore sample and incomplete reporting (Wagner *et al.* 1969, cited in IARC 1993). Similar studies were conducted in Syrian golden hamsters and squirrel monkeys, but the IARC Working Group considered the interpretations questionable because of limited reporting of pathological findings and limited exposure durations (IARC 1993).

Male and female albino Wistar rats (27 per group) and male and female Sherman rats (109 per group) were exposed to aerosols of beryllium sulfate tetrahydrate at a beryllium concentration of 35.8 μg/m^3 for eight hours a day, 5.5 days a week for up to 180 days. Control groups of 69 male and female Wistar rats and 70 male and female Sherman rats were maintained without exposure. The exposed animals developed pulmonary tumors, eight with metastases, that included 18 adenomas, 5 squamous carcinomas, 24 acinous adenocarcinomas, 11 papillary adenocarcinomas, and 7 alveolar cell adenocarcinomas. No control animal had pulmonary tumors (Schepers *et al.* 1957). A similar study was conducted with a group of Sprague-Dawley rats (75 per sex) exposed to beryllium sulfate tetrahydrate at a mean atmospheric concentration of 34.25 ± 23.66 μg/m^3 for seven hours a day, five days a week for 72 weeks. An equal number of rats were exposed to an aerosol of distilled water and used as controls. All surviving exposed rats (43 per group) had alveolar adenocarcinomas. No tumors were found in control rats (Reeves *et al.* 1967, cited in IARC 1993).

Shorter beryllium inhalation exposure regimens also produced lung cancer in rats. Female rats (30 to 50 per group) were exposed to either beryllium oxide or beryllium chloride (concentrations of 0.8, 4, 30, or 400 μg/m^3) for one hour per day, five days per week for four months. A group of 160 females served as controls. In this study, only malignant epithelial cell lung tumors were evaluated. Beryllium exposure caused dose-dependant incidences of malignant epithelial lung tumors, and no lung tumors were observed in

control animals. The total duration of the experiment was not reported (Litvinov *et al.* 1984, cited in IARC 1993).

Three groups of rabbits (sex not specified) were exposed to aerosols of beryllium oxide at beryllium concentrations of 1 μg/L (five rabbits), 6 μg/L (six rabbits), or 30 μg/L (eight rabbits) for five hours per day, five days per week for 9 to 13 months. No control group was used. Lung tumors were not reported, but one of the animals exposed to 6 μg/L for over 11 months had an osteogenic sarcoma in the pubis (Dutra *et al.* 1951, cited in IARC 1993).

In a group of 16 rhesus monkeys (*Macaca mulatta*) exposed to beryllium sulfate aerosol at a beryllium concentration of 35 $\mu g/m^3$, primary anaplastic pulmonary tumors with adenomatous and epidermoid patterns were observed in three animals between six months and eight years after the beginning of exposure. Additional details were not reported (Vorwald 1967, cited in IARC 1993).

In more recent studies, groups of male and female Fischer 344/N rats received single nose-only exposures to beryllium metal sufficient to result in initial lung burdens of approximately 50, 150, or 450 μg of the metal. To this end, animals were exposed to beryllium at concentrations of 470 to 960 mg/m^3 for 10 to 41 minutes. Serial sacrifices were made from 8 to 450 days after the exposure. The target lung burden of 450 μg reduced survival. Beryllium inhalation caused an increased incidence of lung tumors in rats. The most prevalent tumor was bronchiolar/alveolar adenocarcinoma having alveolar, papillary, or tubular patterns, and other tumors included adenosquamous carcinomas and squamous cell carcinomas. Substantial lung tumor multiplicity also was observed (Finch *et al.* 1990a; Haley *et al.* 1990; Finch *et al.* 1991, 1994a, b; all cited in Finch *et al.* 1996).

Tumors were observed in groups of rats receiving initial lung burdens of beryllium metal of 40, 110, 360, and 430 μg by 14 months after exposure began. Approximately 64% of the rats had lung tumors during their lifetimes (Nickell-Brady *et al.* 1994, cited in Finch *et al.* 1996).

The relative susceptibility of A/J mice and C3H/HeJ mice to beryllium-induced pulmonary carcinogenesis was assessed. Mice were exposed to beryllium metal by inhalation to result in mean initial lung burdens of 47 μg beryllium in A/J mice and 64 μg in C3H/HeJ mice. Microscopic analysis of lungs revealed that the tumor incidence in A/J mice was elevated relative to controls (46% for exposed *vs.* 37% for controls), and the A/J mice exhibited greater lung tumor multiplicity. Overall, tumor incidences were lower in C3H/HeJ mice than in A/J mice, and beryllium exposure had little effect (tumor incidence was 5% in beryllium-exposed animals and 10% in controls). Results of statistical analyses of the data were not reported, nor were durations of beryllium exposures (Belinsky *et al.* 1992, Nikula *et al.* 1994, both cited in Finch *et al.* 1996).

Male F344/N rats received single nose-only inhalation exposures to beryllium metal at concentrations sufficient to result in lung burdens of 0.32, 1.8, 10, or 100 μg of beryllium. Rats were sacrificed at 8, 16, 40, 90, 210, and 365 days after exposure. One rat

in the 1.8-μg group, sacrificed after 365 days, had a pulmonary squamous-cell carcinoma. Because the single occurrence of a lung tumor was in an animal from a lower lung burden group, the authors concluded that the tumor was not caused by exposure to beryllium metal (Finch *et al.* 1994c).

4.2 Intratracheal instillation in rats

Female rats received a single intratracheal instillation of 50 μg of beryllium as beryllium hydroxide; then, 10 months later, they received a single instillation of an additional 25 μg. Of the animals sacrificed at 19 months, 13/25 had pulmonary tumors (6 adenomas and 7 carcinomas; one rat had both an epidermoid carcinoma and an adenocarcinoma) (Groth *et al.* 1980, cited in IARC 1993).

Male Wistar rats (10 weeks old) were instilled intratracheally with beryllium oxide once a week for 15 weeks. A group of 16 rats served as untreated controls. The animals were observed until natural death, and 6/30 had lung tumors (two malignant and four benign lung adenomas) (Ishinishi *et al.* 1980, cited in IARC 1993).

Eight groups of inbred albino rats (gender and initial number not specified) received weekly intratracheal instillations of "high-temperature-fired beryllium oxide" (2,000°C) or "low-temperature-fired beryllium oxide" (600°C) at doses of 0.036, 0.36, 3.6, or 18 mg/kg bw. A group of 300 untreated rats served as controls. The animals were observed until natural death. Beryllium calcined at 600°C caused a dose-related increase in the incidence of malignant lung tumors (3/69, 4%; 7/81, 9%; 18/79, 23%; and 8/26, 31%). The high-temperature-treated beryllium was associated with lower incidences of malignant lung tumors (0/76; 0/84; 2/77, 3%; 2/103, 2%). No tumors were found in 104 controls (Litvinov *et al.* 1983, cited in IARC 1993).

4.3 Effects of beryllium metal in p53 knockout mice

Experiments were conducted to assess the sensitivity of $p53^{+/-}$ knockout mice to the carcinogenic effects of metallic beryllium. The $p53^{+/-}$ mouse and other transgenic models are currently under investigation for utility in short-term tests for the assessment of carcinogenic potential (Finch *et al.* 1998b).

Mice of both sexes were exposed to air (negative control), metallic beryllium (target lung burden of 60 or 15 μg), or $^{239}PuO_2$, (target lung burden of 500 or 100 Bq ^{239}Pu) (positive control). Similar exposures of wild-type $p53^{+/+}$ (nontransgenic) mice also were conducted.
The incidences of lung neoplasms are shown in Table 4-1. Gender differences in pulmonary responses of transgenic mice were not apparent; hence, the sexes were pooled for statistical analysis.

Table 4-1. Incidence of mice with one or more pulmonary neoplasms following inhalation exposure to beryllium or Pu

Sex	Heterozygous *p*53$^{+/-}$ mice					Wild-type *p*53$^{+/+}$ mice	
	Air	$^{239}PuO_2$ (500 Bq)	$^{239}PuO_2$ (100 Bq)	beryllium (60 μg)	beryllium (15 μg)	$^{239}PuO_2$ (500 Bq)	beryllium (60 μg)
Male	0/15	1/15	6/15	2/15	0/15	5/15	0/15
Female	0/15	3/14	1/15	2/13	0/14	2/14	0/13
Combined	0/30[a, b, c]	4/29[a]	7/30[b]	4/28[c]	0/29	7/29	0/28[d]

Source: Finch *et al.* (1998a).
[a] Air vs. 500-Bq $^{239}PuO_2$ *p*53$^{+/-}$ mice, $P = 0.052$.
[b] Air vs. 100-Bq $^{239}PuO_2$ *p*53$^{+/-}$ mice, $P = 0.005$.
[c] Air vs. 60-μg beryllium *p*53$^{+/-}$ mice, $P = 0.048$.
[d] 60-μg beryllium *p*53$^{+/-}$ mice vs *p*53$^{+/+}$ mice, $P=0.056$.

For both the heterozygous (*p*53$^{+/-}$) and homozygous (*p*53$^{+/+}$) mice, lung-tumor responses to beryllium and to the positive control agent ($^{239}PuO_2$), were similar, but the latency period for tumor production was reduced in the heterozygous animals, suggesting an increased sensitivity in the transgenic animals.

The incidence of lung tumors in beryllium-exposed *p*53$^{+/-}$ mice was marginally higher than that of beryllium-exposed *p*53$^{+/+}$ mice ($P = 0.056$). Five primary lung neoplasms were observed in the four neoplasm-bearing heterozygous animals in the 60-μg group, while the wild-type animals with the same lung burden developed no tumors during the 22.5 months of the experiment. Heterozygotes exposed to the lower dose of beryllium metal had no lung tumors.

A number of nonpulmonary neoplasms (osteosarcoma, lymphoma, histeocytic sarcoma) also were observed during this experiment but these occurred with similar incidences in exposed and control animals. Therefore, the tumors could not be attributed to administration of either beryllium or $^{239}PuO_2$.

4.4 Intravenous injection in mice and rabbits

In a study reported as an abstract, Cloudman *et al.* (1949, cited in IARC 1993) administered 20 to 22 intravenous injections of either zinc beryllium silicate or beryllium oxide to mice (two injections per week). Beryllium administration caused malignant bone cancer in "some" mice. Similarly in another study (reported as an abstract) Gardner and Heslington (1946, cited in IARC 1993), intravenous administration of these beryllium salts to rabbits at total doses of 1 g caused malignant osteosarcomas, and some of the rabbits had visceral metastases. In a later study (Fodor 1977, cited in IARC 1993), intravenous administration of a beryllium oxide suspension (1% beryllium oxide in 5 mL of physiological saline) caused sarcomas (not otherwise described) in 21/29 (72%) of the animals. The IARC Working Group noted the lack of an appropriate control group and incomplete reporting of this study.

In another study, six groups comprising of 67 rabbits (mixed breeds and sexes) received intravenous injections of zinc beryllium silicate (total doses 1 to 2.1 g) or beryllium silicate (1 to 1.2 g). Injections were administered twice weekly, and the animals' survival was reduced. A group of 10 rabbits were injected with zinc silicate alone (1.2 g) and used as untreated controls. Beryllium exposure caused osteosarcomas in 7/21 animals that survived for more than 30 weeks. The earliest malignant tumor was detected at 32 weeks, and the latest tumor occurred at 83 weeks. No tumors were observed in the control group (Barnes *et al.* 1950, cited in IARC 1993).

In another rabbit study, intravenous injections of beryllium oxide caused osteosarcomas in 6/6 animals that survived for more than 11 months. In this study, rabbits received 360 to 700 mg of beryllium in 20 to 26 injections (three injections per week over six to nine weeks). Six animals survived for at least one year (the total number of animals in the study was not reported), and the first bone tumor was detected after 11.5 months. All six of the surviving animals had osteosarcomas (Dutra and Largent 1950, cited in IARC 1993).

Administration of total doses of 1g of beryllium phosphate, zinc beryllium silicate, or beryllium oxide in divided doses at one- to four-day intervals reduced survival of male and female rabbits, but 7/8 animals that survived for longer than 14 months had osteogenic sarcomas (Hoagland *et al.* 1950, cited in IARC 1993).

Osteosarcomas were produced by intravenous zinc beryllium silicate administration in 10/14 rabbits. Zinc beryllium silicate was administered twice weekly for 10 weeks (for a total dose of 1 g). Animals died or were sacrificed 28 to 57 weeks after the last injection. Tumors were detected 30 to 52 weeks after the last injection (Kelly *et al.* 1961, cited in IARC 1993).

A single intravenous dose of 1g of beryllium phosphate caused osteosarcomas in 2/4 rabbits within 18 months; no tumors were observed in rabbits that were given a single intravenous injection of 1 g of beryllium oxide (Araki *et al.* 1954, cited in IARC 1993). In a similar experiment, a single intravenous dose of 1g of beryllium oxide caused

osteosarcomas in 3/20 rabbits 15 to 18 months after administration (Komitowski 1968, cited in IARC 1993).

4.5 Intraperitoneal injection

Intraperitoneal administration of beryllium sulfate tetrahydrate at 0.02, 0.05, or 0.1 mg/mouse (three times per week for eight weeks) increased the incidences of lung tumors in A/J strain mice, but did not increase tumor multiplicity (Ashby *et al.* 1990, cited in IARC 1993). However, the IARC Working Group noted that the increased incidences were not statistically significant in Fisher's exact test (IARC 1993).

4.6 Implantation and/or injection into bone

After 1 to 43 injections of 10 mg of beryllium oxide as a 1% suspension into the marrow of the femur of rabbits, dosed animals exhibited chondromas, osteomas, chondrosarcomas, and osteochondrosarcomas. Injections were administered twice weekly for up to 22 weeks, and 26/55 (47%) of the animals had bone tumors. The average time between the last injection and the appearance of the tumor was 85 days (Yamaguchi 1963, cited in IARC 1993).

Intramedullary injection of one dose of zinc beryllium silicate powder (20 mg) into the upper end of the tibia of rabbits caused osteosarcomas in 4/12 animals 12 to 15 months after the injection (Tapp 1966, cited in IARC 1993). Implantation of 10 mg of zinc beryllium silicate, beryllium oxide, or beryllium silicate under the periosteum of the tibia also caused bone tumors after 10 to 25 months (Tapp 1969, cited in IARC 1993).

Intramedullary administration of beryllium oxide, beryllium carbonate, and beryllium acetylacetonate to rabbits caused bone tumors within 10 to 17 months (Komitowski 1974, Matsuura 1974, both cited in IARC 1993). Intramedullary administration of either beryllium stearate and beryllium laurate in rabbits did not cause bone tumors (Matsuura 1974, cited in IARC 1993). The doses of beryllium salts administered in the study were not given.

Single intraosseous injections of 0.5 mL of a suspension of 1 g of zinc beryllium silicate in 15 mL of distilled water and gelatin, to yield 33 mg beryllium, caused osteogenic sarcomas in 45/65 rabbits that survived more than four months after the injection. Radiographic examinations indicated that the initial sarcomatous changes occurred after three months (Mazabraud 1975, cited in IARC 1993).

Three groups of male rabbits received implants of pellets of hydroxypropylcellulose mixed with beryllium oxide into the distal metaphysis of the femur as follows: group 1, into the internal callus one week after a fracture (300 mg); group 2, into the bone marrow cavity at a dose of 300 mg; group 3, into the bone marrow cavity at a dose of 50 mg. After 56 weeks, osteosarcomas had developed in 10/10 animals in group 1, 7/10 in group 2, and 1/10 in group 3 (Hiruma 1991, cited in IARC 1993).

4.7 Summary

The results of carcinogenesis studies in experimental animals and reviewed by IARC are summarized in Table 4-2. These studies provide evidence that beryllium and beryllium compounds are carcinogenic to rats, mice, and rabbits. Results of animal experiments have shown consistent increases in lung cancers in rats, mice, and rabbits chronically exposed to beryllium and beryllium compounds by inhalation or intratracheal instillation. Osteocarcinomas have been produced in mice and rabbits exposed to various beryllium salts by intravenous injection or implantation into the bone. IARC has concluded there is sufficient evidence of carcinogenicity in experimental animals for beryllium and beryllium compounds. This conclusion is affirmed by evidence from more recent studies in mice and rats.

Table 4-2. Animal carcinogenesis studies of beryllium metal, alloys, ores, and compounds

Species, strain, and sex	Chemical and physical form	Exposure route, dosage, and regimen	Results and comments*	Reference
Beryllium metal				
Rat, Wistar, F	beryllium metal (100%) 1 to 2.5 µm in saline	intratracheal instillation: 0.5 or 2.5 mg (diameter 1 – 2 µm) in saline x 1 occasion	treated: lung adenomas/adenocarcinomas (first tumor at 8 – 10 mo): low dose 2/21, high dose 9/16 ($P < 0.008$) controls: no tumors	Groth *et al.* (1980)
Rabbit, n.s., n.s.	beryllium metal "finely divided"	Intravenous injection: 40 mg x 1 occasion	of 24 subjects: 9 died with liver necrosis within 7 d and 10 more within 1 mo, 2 died with pulmonary infections, 2 had "characteristic bone sarcomata," and 1 was unaffected controls: no controls	Barnes (1950 [letter])
Beryllium alloys				
Rat, Wistar, F	Be 99%:Cr Be 62%:Al 38% Be 04%: Cu Be 02%:Ni 98% Be 24%: Cu 0.4%:Co 96%	intratracheal instillation: 0.5 or 2.5 mg (diameter 1 – 2 µm) in saline x 1 occasion	treated: lung adenomas/adenocarcinomas (first tumor at 8 – 10 mo): Be:Cr, low dose 7/20, high dose 9/26 ($P < 0.008$), Be:Al, low dose 1/21, high dose 4/24 ($P < 0.008$); other alloys, no tumors controls: no tumors	Groth *et al.* (1980)
Beryllium ores				
Rat, Greenacres Controlled Flora and Charles River Caesarian, n.s.	beryl ore (diam. 0.64 µm) = 210 µg/m^3 Be Bertrandite ore (diam. 0.27 µm) = 620 µg/m^3 Be	inhalation: dust, 15 mg/m^3/6 h/d, 5 d/wk, (up to) 17 mo	beryl ore: after 12 mo; 5/11 squamous metaplasia or small epidermoid tumors; after 17 mo, 18/19 lung tumors (18 bronchiolar alveolar-cell tumors [BACs]), 7 adenomas, 9 adenocarcinomas, and 4 epidermoid tumors) bertrandite ore: granulomas, but no tumors controls: no lesions of any type (IARC noted high crystalline silica content of bertrandite and incomplete reporting)	Wagner *et al.* (1969)
Hamster, Syrian golden, n.s.	beryl ore (diam. 0.64 µm) = 210 µg/m^3 Be Bertrandite ore (diam. 0.27 µm) = 620 µg/m^3 Be	inhalation: dust, 15 mg/m^3 for 6 h/d, 5 d/wk, (up to) 17 mo	beryl ore and bertrandite ore: atypical proliferations in lungs after 12 mo (some thought to be BACs); lesions bigger and more adenomatous after 17 mo in the beryl ore group controls: no pulmonary lesions (IARC noted high crystalline silica content of bertrandite and incomplete reporting)	Wagner *et al.* (1969)

Species, strain, and sex	Chemical and physical form	Exposure route, dosage, and regimen	Results and comments*	Reference
Monkey, *Saimiri sciurea*, M	Beryl ore (diam. 0.64 µm) = 210 µg/m^3 beryllium Bertrandite ore (diam. 0.27 µm) = 620 µg/m^3 beryllium	inhalation: dust, 15 mg/m^3 6 h/d, 5 d/wk, (up to) 23 mo	beryl ore and bertrandite ore: death rate exceeded controls by 11%; some bronchiolar inflammation noted in treated groups; no tumors observed controls: no pulmonary lesions (IARC noted incomplete reporting and limited duration of study)	Wagner *et al.* (1969)
Beryllium compounds				
Rat, Long-Evans (BLU:LE), M and F	beryllium sulfate	oral: 5 ppm (5 mg/L) in drinking water (also contained 5 ppm chromium [III] acetate, 50 ppm zinc acetate, 5 ppm copper acetate, 10 ppm manganese chloride, 1 ppm cobalt chloride, and 1 ppm sodium molybdate) given *ad libitum* until natural death	treated and controls: 20% to 30%, of both groups died from pneumonia; "no significant difference in tumor incidence was observed between treated and control groups." (IARC noted that the dose was too low for an evaluation of carcinogenicity)	Schroeder & Mitchner (1975)
Rat, Wistar, M and F Rat, Sherman M and F	beryllium sulfate tetrahydrate	inhalation: aerosol, 35.8 µg/m^3 8 h/d, 5.5 d/wk, 180 d and (those surviving) then placed in normal air for up to 72 wk	treated: 76 lung tumors found, 8 metastatic: 8 adenomas, 5 squamous cell carcinomas, 24 acinous adenocarcinomas, 11 papillary adenocarcinomas, and 7 alveolar-cell adenocarcinomas controls: no lung tumors (IARC noted incomplete reporting of the study)	Schepers *et al.* (1957)
Rat, Sprague-Dawley CD, M and F	beryllium sulfate tetrahydrate (diam. 0.12 µm)	inhalation: aerosol, 34 µg/m^3, 7 h/d, 5 d/wk, 72 wk	treated: 1st lung tumor seen at 9 mo; all surviving 13 mo or more had tumors (some multiple) and all were alveolar adenocarcinomas controls: no lung tumors (IARC noted incomplete reporting of the study)	Reeves *et al.* (1967)
Rat, albino, F	beryllium oxide or beryllium chloride	inhalation: aerosol, 0.8, 4, 30, or 400 µg/m^3, 1 h/d, 5 d/wk, 16 wk	treated: malignant epithelial lung tumors were scored: respectively, for doses): beryllium oxide: 3/44, 4/39, 6/26, and 8/21; beryllium chloride: 1/44, 2/42, 8/24, and 11/19 controls: no lung tumors	Litvinov *et al.* (1984)
Rabbit, n.s, n.s.	beryllium oxide (diam. 0.29 µm)	inhalation: aerosol, 1, 6, or 30 µg/L, 5 h/d, 5 d/wk, 36 – 72 wk	treated: 1 metastatic osteogenic sarcoma was observed in an animal exposed to 6 µg for 235 d controls: no controls (IARC noted the small number of animals and limited study duration)	Dutra *et al.* (1951)

Species, strain, and sex	Chemical and physical form	Exposure route, dosage, and regimen	Results and comments*	Reference
Monkey, Rhesus (*Macaca mulatta*), n.s.	beryllium sulfate	inhalation: aerosol, 35 µg/m^3, "for a long time"	treated: 3 animals developed primary anaplastic pulmonary tumors with adenomatous and epidermoid patterns between 6 mo and 8 yr after exposure controls: no controls	Vorwald (1967)
Rat, Wistar-derived, F	beryllium hydroxide	intratracheal instillation: 50 µg Be in distilled water x 1 occasion, followed (after 40 wk) by another 2.5 µg	treated: animals were sacrificed after 64 wk; 13/25 had pulmonary tumors (6 adenomas and 7 adenocarcinomas) and 1 had both epidermoid carcinoma and adenocarcinoma controls: no untreated controls (IARC noted the lack of an appropriate control group)	Groth *et al.* (1980)
Rats, Wistar, n.s.	beryllium oxide (low-fired, 900°C) arsenic trioxide	intratracheal instillation: 1 mg/wk as Be (or As), 15 wk and then observed for life	treated: beryllium oxide: lung tumors: 1 squamous-cell carcinoma, 1 adenocarcinoma, and 4 adenomas ("3 suspected of malignancy") arsenic trioxide: 1 squamous-cell carcinoma controls: no lung tumors	Ishinishi *et al.* (1980)
Rats, inbred albino, n.s.	beryllium oxide (l) (low-fired, 600°C) beryllium oxide (h) (high-fired, 2,000°C)	intratracheal instillation: single doses of 0.04, 0.4, 4.0 and 18 mg/kg bw and then observed for life	treated: malignant epithelial lung tumors (respectively, for doses): BeO (l): 0/76, 0/84, 2/77, and 2/103 BeO(h): 3/69, 7/81, 18/79 and 8/26 controls: no lung tumors	Litvinov *et al.* (1983)
Monkey, *Macaca mulatta*, n.s.	beryllium oxide ("particles" in saline)	intrabronchial intubation and/or (n.s.) bronchomural injection, single dose n.s.	treated: "1st bronchogenic tumor detected about 4.5 yr after treatment; at about 5.5 yr, 2 monkeys developed highly neoplastic tumors with adenomatous and epidermoid patterns"	Vorwald (1967)
Mouse, n.s., n.s.	zinc beryllium silicate (8.4 mg Zn, 0.26 mg Be) zinc silicate (2.8 mg Zn) beryllium oxide (1.5 mg Be)	intravenous injection: 20 – 22 injections (2/wk)	treated: "some mice receiving Zn Be silicate developed bone tumours" controls: no tumors	Cloudman *et al.* (1949 [abstract])
Rabbit, n.s., n.s.	zinc beryllium silicate (diameter $\leq$ 3 µm) beryllium oxide (diameter $\leq$ 3 µm)	intravenous injection: 20 doses totaling 1 g/6 wk	treated: Zn Be silicate: "all 7 surviving rabbits developed malignant osteosarcomas (4 of them metastatic)"; BeO: "1 rabbit, sacrificed at 1 yr, had a malignant osteosarcoma" controls: "no such tumors were induced by administration of 65 other minerals in the same way"	Gardner and Heslington (1946 [abstract])
Rabbit, n.s., n.s.	zinc beryllium silicate (550 mg Zn, 17 mg Be) zinc silicate (390 mg Zn) beryllium oxide (390 mg Be)	intravenous injection: 20 – 22 injections (2/wk)	treated: "4 of 5 rabbits given Zn Be silicate and surviving past 1 yr developed bone tumors, 3 with metastases" controls: n.s.	Cloudman *et al.* (1949 [abstract])

Species, strain, and sex	Chemical and physical form	Exposure route, dosage, and regimen	Results and comments*	Reference
Rabbit, n.s, n.s.	zinc beryllium silicate (2% BeO) (diameter $\leq$5 µm) Beryllium silicate (diameter $\leq$5 µm)	intravenous injection: at various concentrations in water (1.0, 1.2, or 2.0 g total), in 6 – 10 injections, 2/wk	treated: Zn Be silicate, Be silicate: 7/21 rabbits injected with Be silicates (surviving 30 wk) developed bone sarcomas; earliest malignant tumor seen at 32 wk and latest at 83 wk controls: no tumors found in rabbits injected with Zn silicate (IARC noted survival was poor in the study)	Barnes *et al.* (1950)
Rabbit, n.s., M and F	beryllium oxide (highly purified) (diameter $\leq$1 µm) calcined phosphor (containing beryllium oxide, zinc oxide, and silica in M ratio of 1:1:1) (diameter $\leq$5 µm)	intravenous injection: Be oxide total 360 – 700 mg Be/rabbit in 20 – 26 injections and phosphor total 64 – 90 mg Be/ rabbit in 17 – 25 injections, 3/wk, x 6 – 9 wk	treated: BeO: 6/6 (surviving) rabbits had osteosarcomas (some primary, some metastatic, and some multiple) after 1 yr; phosphor: 2/3 (surviving) rabbits had osteosarcomas after 1 yr controls: "about 50 untreated rabbits, kept for similar periods, developed no tumor" (IARC noted small group sizes, limited reporting, and incomplete observations)	Dutra and Largent (1950)
Rabbit, n.s., M&F	beryllium phosphate zinc beryllium silicate (2.3% BeO) zinc beryllium silicate (14% BeO) beryllium oxide	intravenous injection: 1% suspension in saline, at 1- or 4-d intervals, to deliver a total of 1 g of compound per rabbit	treated: 7/8 surviving rabbits developed osteogenic sarcomas; Be phosphate; 1 survivor received only 100 mg and had no tumor; Zn Be silicate (2.3% BeO): 3 had tumors; Zn Be silicate (14% BeO): 3 with tumors; BeO: 1 had a tumor controls: n.s. (IARC noted small group sizes and lack of appropriate controls)	Hoagland *et al.* (1950)
Rabbit, n.s., n.s.	beryllium phosphate beryllium oxide beryllium oxide mixed with zinc oxide, manganese oxide, and/or silicon oxide	intravenous injection: single doses of 1 g per animal	treated: Be phosphate: 2/4 rabbits had osteosarcomas within 18 mo; BeO: no tumors found in 3 rabbits; BeO mixed with other oxides: 9/31 developed osteosarcomas controls: n.s. (IARC noted small group sizes, lack of appropriate controls, and incomplete observations)	Araki *et al.* (1954)
Rabbit, n.s., M	zinc beryllium silicate (3.4% BeO)	intravenous injection: 2/wk, 10 wk, for a total dose of 1 g (33.6 mg BeO)	treated: 5 rabbits developed osteogenic sarcomas after 9 to 11 mo controls: n.s. (IARC noted small group size and lack of appropriate controls)	Janes *et al.* (1954)
Rabbit, n.s., n.s.	zinc beryllium silicate (diameter 1 – 3 µm)	intravenous injection: 2/wk, 10 wk, for a total dose of 1 g	treated: rabbits died or were killed 28 – 57 wk after last injection; osteogenic sarcomas developed in 10/14 rabbits after 30 – 52 wk controls: n.s. (IARC noted small group size and lack of appropriate controls)	Kelly *et al.* (1961)
Rabbit, n.s., n.s.	beryllium oxide	intravenous injection: BeO in a 1% saline suspension, x 1 occasion, for a total dose of 1 g	treated: osteosarcomas were induced in 3/20 rabbits 15 – 18 mo after injection controls: n.s. (IARC noted the lack of appropriate controls)	Komitowski (1968)

Species, strain, and sex	Chemical and physical form	Exposure route, dosage, and regimen	Results and comments*	Reference
Rabbit, n.s., n.s.	beryllium oxide	intravenous injection: BeO in a 1% saline suspension, 1/wk, 25 wk	treated: sarcomas were induced in 21/29 rabbits surviving to "the end of the experiment" controls: n.s. (IARC noted the lack of appropriate controls and incomplete reporting)	Fodor (1977)
Mouse, A/J, M	beryllium sulfate tetrahydrate (purity $\geq$ 99%) suspended in water	intraperitoneal injection: maximum total dose of 0.02, 0.05, or 0.1 mg/mouse 3/wk, 8 wk	treated: authors stated treatment produced significant (X^2 analysis) increases in lung tumor incidences at total dose of 1.2 and 2.4 mg/mouse without a significant increase in tumor multiplicity controls: water only; tumor incidence n.s. (IARC noted that the increases in tumor incidence were not significant using Fisher's exact test)	Ashby *et al.* (1990)
Rabbit, n.s., n.s.	beryllium oxide	injection into bone: 10-mg doses (1% in saline), injected into the bone marrow of the femur, 2/wk for up to 23 wk	treated: 1/55 rabbits had a chondroma, 3/55 had osteomas, 15/55 had chondrosarcomas, and 7/55 had osteochondrosarcomas after 1 to 2 yr; the average period between last injection and tumor occurrence was 85 days controls: n.s.	Yamaguchi (1963)
Rabbit, n.s., n.s.	zinc beryllium silicate (powder, diameter $\leq$ 5 µm)	implantation into bone: 20 mg given as a single intramedullary injection into the right tibia; as a control, Zn oxide injected into the left tibia	treated: at 15 – 20 mo after implantation, 4/12 had osteogenic sarcomas (3 metastasized), 4/12 were killed at 15 – 20 mo with no evidence (clinical or radiological) of tumors, and 4/12 had died from in intercurrent infections controls: no effect was seen from Zn oxide	Tapp (1966)
Rabbit, n.s., n.s.	zinc beryllium silicate beryllium oxide beryllium silicate	implantation into bone: 10 mg implanted on a single occasion under the periosteum of the right tibia; as a control, Zn oxide or Zn silicate implanted on the left side	treated: Zn Be silicate: 1/6 rabbits developed a metastatic, osteogenic sarcoma; BeO: 2/6 had metastatic, osteogenic sarcomas; and Be silicate: 1/6 had an osteogenic sarcoma (the tumors were observed in these rabbits 10 – 25 months after implantation controls: no effect was seen from Zn oxide	Tapp (1969)
Rabbit, n.s., n.s.	beryllium oxide (diameter ~4 µm)	injection into bone: intramedullary injection in gelatin into the femur (amount and schedule, n.s.)	treated: 5/20 rabbits osteogenic sarcomas within 2nd yr; the 1st tumor was observed 13 mo after injection controls: n.s. (IARC noted the lack of appropriate controls and incomplete reporting)	Komitowski (1974)

Species, strain, and sex	Chemical and physical form	Exposure route, dosage, and regimen	Results and comments*	Reference
Rabbit, n.s., n.s.	beryllium carbonate beryllium acetate beryllium acetylacetonate beryllium laurate beryllium stearate	injection into bone: intramedullary injection (amounts, placement, and schedule, n.s.)	treated: Be carbonate: 30/173 developed osteosarcomas 10 – 13 mo after implantation; Be acetate: n.s.; Be acetylacetonate: 1/10 (that survived 13 mo) developed an osteosarcoma; Be laurate: n.s.; and Be stearate: n.s. controls: n.s. (IARC noted small group sizes, except for Be carbonate, and incomplete reporting)	Matsuura (1974)
Rabbit, Fauve de Bourgogne, n.s.	zinc beryllium silicate	injection into bone: 1 g (33 mg Be) in gelatin suspension injected x 1 occasion into the tibial or femoral metaphysis	treated: 45/65 rabbits surviving more than 4 mo after injection developed osteogenic sarcomas; radiographic examination showed that the earliest sarcomatous changes occurred within 3 mo of injection controls: n.s. (IARC noted the lack of appropriate controls)	Mazabraud (1975)
Rabbit, n.s., n.s.	beryllium oxide	implantation into bone: pellets of hydroxypropylcellulose mixed with BeO implanted into the distal metaphysis of the femur according to experimental group: (1) internal callus artificial fracture at 300 mg, (2) bone marrow cavity at 300 mg, (3) bone marrow cavity at 50 mg, and (4) untreated	treated: group (1): 56 weeks post implantation, osteosarcomas had developed in 10/10 rabbits; these tumors appeared significantly earlier than those in other groups; group (2): 7/10 had osteosarcomas; group (3): 1/10 had osteosarcomas; (for all groups: 80% of rabbits with primaries had lung metastases as well) controls: n.s.	Hiruma (1981)
Mouse, SENECAR, M&F	beryllium sulfate (purity n.s.)	intraperitoneal injection (followed by) dermal applications of 12-*O*-tetradecanoylphorbol 13-acetate (TPA) co-treatment: in saline, 0, 0.01, 0.1, 1.0, 5.0, or 10.0 µg/mouse; 1 wk after Be sulfate injection, TPA applied, dermally, 2/wk for 26 wk; a positive control group was dosed with 50.5 µg/mouse benzo[a]pyrene followed by TPA treatment	treated: "failed to induce a significant number of mouse skin papillomas"	Nesnow (1985)

Source: IARC (1993).

M = males; F = females; n.s. = not specified. *****Significant increase (Fisher's exact test, 1-tailed).

5 Genotoxicity

5.1 Prokaryotic systems

5.1.1 Induction of mutations in Salmonella typhimurium

Beryllium compounds (beryllium chloride, beryllium nitrate, beryllium sulfate) were not mutagenic when tested in a variety of *Salmonella* tester strains, in the presence or absence of exogenous metabolic activation (IARC 1993) (Appendix A, Table 19).

Beryllium sulfate was not mutagenic when tested in five *S. typhimurium* strains, in the presence or absence of metabolic activation by S9 liver homogenate (Ashby *et al.* 1990). A review of the literature by these authors, indicates that a number of earlier *Salmonella* studies on beryllium sulfate and beryllium nitrate failed to detect mutagenic activity. In these studies, TA1530, TA1535, TA1536, TA1537, TA1538, TA98, and TA100 strains of *S. typhimurium* were tested at beryllium sulfate concentrations that ranged from 25 to 5,000 μg/plate. The LT2 and TA100 strains of *S. typhimurium* were tested with beryllium nitrate at a concentration of 10^{-4} to 10^{-1} M.

Beryllium was non-mutagenic to *S. typhimurium* strains TA100 and TA98 at concentrations of > 5,000 μg/plate (beryllium chloride), > 5,000 μg/plate (beryllium nitrate), and > 0.43 μg/plate (beryllium oxide), in the presence and absence of S9 rat liver homogenate (Kuroda et al. 1991).

5.1.2 Induction of mutation in Escherichia coli

Beryllium chloride induced a forward mutation in one test with *E. coli*, in the absence of exogenous metabolic activation, but tested negative with beryllium sulfate for differential toxicity with or without exogenous metabolic activation (IARC 1993) (Appendix A, Table 19).

5.1.3 Induction of differential toxicity in Bacillus subtilis rec *assay*

Beryllium chloride (375, 750, and 1,500 μg/disk), beryllium nitrate (375, 750, and 1,500 μg/disk), and beryllium oxide (0.1 μg/disk) were tested in the *B. subtilis rec* assay. Evidence of a weak DNA-damaging effect was noted for beryllium chloride and beryllium nitrate. Beryllium oxide was negative in the *rec* assay, which was attributed to the incomplete solubility of the compound in water (Kuroda *et al.* 1991).

Beryllium compounds (beryllium nitrate, beryllium sulfate, beryllium oxide) were found to be DNA damaging and tested positive in the *B. subtilis rec* assays, in the absence of exogenous metabolic activation (IARC 1993) (Appendix A, Table 19).

5.1.4 Induction of mutation in Saccharomyces cerevisiae

Beryllium sulfate failed to induce mitotic recombination in *S. cerevisiae*, in the presence or absence of exogenous metabolic activation (IARC 1993) (Appendix A, Table 19).

5.2 Mammalian systems

5.2.1 In vitro *assays*

5.2.1.1 hprt *locus forward mutation test*

Beryllium chloride was positive in the *hprt locus* gene mutation test in Chinese hamster lung V79 cells in the absence of exogenous metabolic activation (IARC 1993) (Appendix A, Table 19).

5.2.1.2 Mammalian cell transformation assays

Beryllium compounds in the absence of exogenous metabolic activation, were found to be mutagenic causing cell transformations in murine, Syrian hamster embryo cells, rat embryo cells (beryllium sulfate), and rat tracheal epithelial cells (beryllium oxide) (IARC 1993) (Appendix A, Table 19).

5.2.1.3 Sister chromatid exchanges (SCEs)

Beryllium chloride (31 to 250 μg/mL), beryllium nitrate (31 to 500 μg/mL), and beryllium oxide (0.02 to 0.09 μg/mL) were tested for induction of SCEs in Chinese hamster lung V79 cells. Beryllium chloride and beryllium nitrate induced significant SCEs in the presence of S9 rat liver homogenate. Beryllium oxide tested negative for induction of SCEs (Kuroda *et al.* 1991).

Beryllium compounds were found to damage chromosomes and tested positive for SCEs in Chinese hamster lung V79 cells (0.05 and 0.25 μg/mL beryllium nitrate), Syrian hamster embryo cells (beryllium sulfate), and human lymphocytes (0.05 μg/mL beryllium sulfate); in the absence of exogenous metabolic activation (IARC 1993) (Appendix A, Table 19).

5.2.1.4 Chromosomal aberrations tests

In studies reviewed by IARC (1993), beryllium compounds (beryllium nitrate, beryllium sulfate, beryllium oxide) were found to damage chromosomes and tested positive for chromosomal aberrations in swine lymphocytes (beryllium chloride), Chinese golden hamster ovary cells (beryllium sulfate), Syrian hamster embryo cells (beryllium sulfate), and human lymphocytes (beryllium sulfate); in the absence of exogenous metabolic activation (Appendix A, Table 19).

When beryllium sulfate (0.2 and 1.0 mM) was tested for the induction of chromosomal aberrations in Chinese hamster ovary cells, it yielded equivocal results (Brooks *et al.* 1989). Using Chinese hamster lung cells, Ashby *et al.* (1990) failed to note any evidence of a clastogenic response for beryllium sulfate (0.078, 0.156, 0.313, 0.625 μg/mL), either in the presence or absence of an Aroclor-induced S9 rat liver homogenate.

5.2.1.5 DNA damage/repair tests

DNA single strand breaks

Beryllium oxide was found to damage DNA and tested positive for DNA single strand breaks in rat tracheal epithelial cells (IARC 1993) (Appendix A, Table 19).

Unscheduled DNA synthesis

Beryllium sulfate was found to be DNA damaging and tested positive for unscheduled DNA synthesis (UDS) in primary rat hepatocytes (IARC 1993) (Appendix A, Table 19).

5.2.2 In vivo *assays*

5.2.2.1 Host-mediated assay

Beryllium sulfate was not mutagenic in *S. typhimurium* and *S. cerevisiae* host-mediated assays in mice (IARC 1993) (Appendix A, Table 19).

5.2.2.2 Micronucleus test

Ashby *et al.* (1990) performed an analysis of micronuclei induction using beryllium sulfate administered by gavage in saline at doses of 1.45 g/kg or 2.3 g/kg. $BeSO_4$ failed to induce micronucleated polychromatic erythrocytes (MPE) in the bone marrow of male CBA mice.

5.2.2.3 Oncogene transformation assays

Nickell-Brady *et al.* (1994) examined pulmonary adenocarcinomas induced by beryllium metal for the presence of genetic alteration in the K-*ras*, *p53*, and c-*raf*-1 genes. No K-*ras* codon 12, 13, or 61 mutations were seen in 24 lung tumors examined by direct sequencing. Using a more sensitive assay that detects mutant alleles at a sensitivity of $1x10^{-3}$, K-*ras* codon 12 GGT-GTT transversions were found in 2 of 12 adenocarcinomas. The researchers suggested "these activations were a late and rare event, possibly stemming from genomic instability during tumor progression." Nuclear immunoreactivity of *p53* was not observed in any beryllium-induced tumor, nor were any mutations detected within exons 5-8 of the *p53* gene. No rearrangements of the c-*raf*-1 protooncogene were detected by Southern blot analysis. The authors concluded that the mechanisms underlying the development of beryllium-induced lung cancer in rats did not involve gene dysfunctions commonly associated with human non-small-cell lung cancer.

5.3 Summary

Beryllium compounds were not mutagenic when tested in a variety of *Salmonella* tester strains. However, beryllium compounds were positive for *hprt locus* gene mutation in hamster cells and caused cell transformations in mammalian cells *in vitro*. Beryllium compounds also induced genetic alteration in the K-*ras* gene, without affecting *p53* or rearrangements of the c-*raf*-1 protooncogene, in beryllium-induced tumor cells. Beryllium compounds are clastogenic, inducing differential toxicity in *B. subtilis*; SCEs in hamster, rat, and human cells, *in vitro*; chromosomal aberrations in swine, hamster, and human cells, *in vitro*; and single strand chromosomal breaks and UDS in rat cells, *in*

vitro. However, beryllium compounds tested equivocally for the induction of forward mutation in *E. coli* and failed to induce mitotic recombination in *S. cerevisiae, in vitro,* or micronuclei in mice, *in vivo*.

6 Other Relevant Data

6.1 Absorption, distribution, metabolism and excretion

Data available to the IARC Working Group concerning absorption, distribution, metabolism, and excretion indicated that beryllium, when administered orally, beryllium is absorbed from the gastrointestinal tracts of mice, rats, dogs, and monkeys. After oral administration of carrier-free ^{7}Be as a chloride, 0.6% of the dose was estimated to be absorbed in monkeys, although the urinary excretion was reported to be 3.71%. Beryllium was excreted in the urine of these species for two days post-administration (Furchner *et al.* 1973, cited in IARC 1993).

Continuous inhalation of beryllium sulfate by rats resulted in development of a lung burden plateau after approximately 36 weeks (Reeves and Vorwald 1967, cited in IARC 1993). Clearance from lungs included accumulation of beryllium in the tracheobronchial lymph nodes, where concentrations reached peak values at 52 weeks after cessation of inhalation exposure. Deposition in other organ systems was not reported. In a later study, however, Zorn *et al.* (1977, cited in IARC 1993) reported that inhalation (nose-only) of aqueous aerosols of beryllium chloride and beryllium sulfate by rats resulted in approximately 13.5% of the dose being deposited in the skeleton.

When dogs inhaled aerosols of beryllium oxide calcined at 500°C (low-fired) or 1,000°C (high-fired), clearance from the lung followed first-order kinetics. Clearance half-time was 240 days for high-fired beryllium oxide and 64 days for the low-fired compound. Beryllium was distributed to the skeleton, tracheobronchial lymph nodes, liver, and blood. Both gastrointestinal and urinary excretions of beryllium were reported (Finch *et al.* 1990b, cited in IARC 1993).

During inhalation carcinogenicity studies of beryl ore dusts (described in Section 4), Wagner *et al.* (1969, cited in IARC 1993) reported elevated levels of beryllium in skeletons of rats, hamsters, and monkeys.

Like inhaled beryllium, parenterally administered beryllium salts lead to accumulation of the metal in the skeletal system. One day after intramuscular injection of beryllium chloride to rats, the highest concentrations of beryllium were detected in skeleton, liver, kidney, lungs, and spleen. After 64 days, skeletal and splenic beryllium concentrations were still higher, indicating continued deposition in these tissues, while concentrations in other tissues were reduced (Crowley *et al.* 1949). Similar results were reported in a comparative study for rats, and, to a lesser extent, for rabbits (Scott *et al.* 1950, cited in IARC 1993).

Twenty-four hours after intravenous administration of beryllium chloride (at pH 2) to rats, nearly half (47%) the administered dose was excreted in the urine and 43% was detected in bone. Only 4% of the administered dose remained in the liver, and 0.1% was recovered from the spleen (Klemperer *et al.* 1952, cited in IARC 1993).

After intravenous administration of beryllium sulfate to rats, circulating beryllium in the plasma was largely bound to plasma globulins, and a small part of the dose remained in a low-molecular-weight form (Vacher and Stoner 1968, cited in IARC 1993). Similar binding of beryllium to plasma proteins has been demonstrated for guinea pigs (Stiefel *et al.* 1980, cited in IARC 1993). When beryllium chloride was added to normal plasma (*in vitro*), only 2.5% was dialyzable, indicating a high level of binding to macromolecules. Other beryllium salts, however, were more readily dialyzable from plasma (citrate, 62%; maleate, 30%; bicarbonate, 10%). Feldman *et al.* (1953, cited in IARC 1993) concluded that at plasma concentrations in excess 10^{-7} mol/L, most of the beryllium present is in a nondialyzable phosphate state, with the smaller, dialyzable portion being mainly citrate. A low-affinity binding site for beryllium also was observed on the outer cell surface of human and guinea pig lymphocytes, and a higher-affinity binding site was detected in the cell nucleus (Skilleter and Price 1984, cited in IARC 1993).

After beryllium sulfate was repeatedly administered intraperitoneally to rats, beryllium was found concentrated in the cells of the proximal convoluted tubules (Berry *et al.* 1987, 1989, cited in IARC 1993). Beryllium accumulated in hepatic lysosomes where it was dissociated to the ionic form (Be^{2+}) by lysozymes and then became detectable in proximal nuclei of rats (Levi-Setti *et al.* 1988, Magos 1991, both cited in IARC 1993). Beryllium exhibited an affinity for nuclei isolated from rat liver, but was not bound to DNA or histones, only to a highly phosphorylated, non-histone protein fraction (Witschi and Aldridge 1968, Parker and Stevens 1979, both cited in IARC 1993).

Snow (1992) reviewed the effects of beryllium on cellular immunity and nucleic acid metabolism and suggested that a number of biological activities of beryllium resemble those attributed to metals known to be carcinogenic such as nickel and chromium. For example, all elicit strong immune responses in the respiratory system, and all affect enzymes involved in nucleotide metabolism and can decrease the fidelity of DNA replication *in vitro*. Epidemiological studies of occupational exposures have not generally benefited from reliable bio-exposure data. Although beryllium can be measured in blood or urine (see section 2), temporal relationships are unclear; current or recent exposure levels are not distinguishable because urinary excretion of beryllium can continue for several years following a known exposure (Klemperer *et al*. 1951, De Nardi *et al*. 1953, both cited in Leonard and Bernard 1993).

6.2 Binding to nucleoproteins and interference with DNA synthesis

Experimental studies in guinea pigs have demonstrated that ionized beryllium can bind to nucleic acids (Lansdown 1995, Leonard and Lauwerys 1987). In addition to binding to nucleoproteins, beryllium compounds (beryllium chloride and beryllium sulfate) affect certain enzymes (DNA and RNA polymerases, deoxythymidine kinase, and deoxythymidylate deaminase) needed for DNA synthesis. These effects can produce infidelity in DNA replication *in vitro* that may be manifested as genetic transformations in microorganisms and mammalian cells (Leonard and Lauwerys 1987).

6.3 Summary

After administration by inhalation, beryllium compounds are absorbed into the systemic circulation in studies involving mice, rats, guinea pigs, dogs, and monkeys. Pharmacokinetic analysis of beryllium compounds administered either by inhalation or intratracheally provided evidence that these beryllium compounds accumulate in the lung. Beryllium also accumulates in the bone after administration by inhalation or injection. Clearance from the bone is slower than from other organs. Absorbed beryllium is excreted by both gastrointestinal and urinary routes. Beryllium can bind to nucleic acids and affects certain enzymes needed for DNA synthesis.

7 References

1. Angerer, J. and K.H. Schaller, eds. (1985). *Analysis of Hazardous Substances in Biological Materials.* Vol. 1, Weinhein, VCH Verlagsgesellschaft, pp. 57-65.

2. Apostoli, P., S. Porru, and L. Alessio. (1989). Behaviour of urinary beryllium in general population and in subjects with low-level occupational exposure. *Med Lav* 80:390-396.

3. Araki, M., S. Okada, and Fijita.M. (1954). Beryllium. Experimental studies on beryllium-induced malignant tumours of rabbits (Jpn.). *Gann* 45:449-451.

4. Ashby, J., M.J. Ishidate, G.D. Stoner, M.A. Morgan, F. Ratpan, and R.D. Callander. (1990). Studies on the genotoxicity of beryllium sulphate in vitro and in vivo. *Mutat Res* 240:217-225.

5. ATSDR. (1993). *Toxicological profile for beryllium: Update.* U.S. Department of Health and Human Services., Public Health Service., Agency for Toxic Substances and Disease Registry, Atlanta., GA., Division of Toxicology, Toxicology Information Branch.

6. Barnard, A.E., K.J. Torma-Krajewski, and S.M. Viet. (1996). Retrospective beryllium exposure assessment at the Rocky Flats Environmental Technology Site. *Am Ind Hyg Assoc J* 57:804-808.

7. Barnes, J.M., F.A. Denz, and H.A. Sissons. (1950). Beryllium bone sarcomata in rabbits. *Br J Cancer* 4:212-222.

8. Belinsky, S. A., K.J. Nikula, and G.L. Finch. (1992). *Comparative pulmonary tumorigenicity of NNK and beryllium in strain A and C3H mice.* Finch, G. L., Nikula, K. J., and Bradley, P. L. (eds.). LMF-138, 149-150. Springfield, VA, National Technical Information Service. Inhalation Toxicology Research Institute Annual Report 1991-1992.

9. Berry, J.-P., F. Escaig, and P. Galle. (1987). Study of intracellular localization of beryllium by analytical ionic microscopy (Fr.). *CR Acad Sci Paris* 304:239-243.

10. Berry, J.-P., P. Mentre, P. Hallegot, R. Levi-Setti, and P. Galle. (1989). Cytochemical study of abnormal intranuclear structures rich in beryllium. *Biol Cell* 67:147-157.

11. Bioana, J.M. (1980). *Technical Assistance Report*: Walter Reed Army Medical Center, Washington, DC (NIOSH Report No. TA-80-60-756), Cincinnati, OH, National Institute for Occupational Safety and Health.

12. BISAC. (1997). Is beryllium carcinogenic in humans? Beryllium Industry Scientific Advisory Committee. *J Occup Environ Med* 39:205-208.

13. Bobrischev-Pushkin, D.M., L.A. Naumova, A.A. Grinberg, and N.A. Khelkovsky-Sergeyev. (1975). Detection of different beryllium compounds at different types of welding (Rus. with Eng. summary). *Gig Tr Prof Zabol* 2:41-43.

14. Boffetta, P. (1993). Carcinogenicity of trace-elements with reference to evaluations made by the International Agency for Research on Cancer. *Scand J Work Environ Health* 19(Suppl 1):67-70.

15. Breslin, A.J. and W.B. Harris. (1959). Health protection in beryllium facilities. Summary of ten years of experience. *Arch Ind Health* 19:596-648.

16. Brooks, A.L., W.C. Griffith, N.F. Johnson, G.L. Finch, and R.G. Cuddihy. (1989). The induction of chromosome damage in CHO cells by beryllium and radiation given alone and in combination. *Radiat Res* 120:494-507.

17. Buckley J.D., Pendergrass T.W., Buckley C.M., Pritchard D.J., Nesbit M.E., Provisor A.J., and Robison L.L. (1998). Epidemiology of osteosarcoma and Ewing's sarcoma in childhood: A study of 305 cases by the children's cancer group. *Cancer* 83(7):1440-1448.

18. Budavari, S., M.J. O'Neil, A. Smith, and P.E. Heckelman. (1996). *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*. Whitehouse Station, NJ. Merck & Company.

19. Carpenter, A.V., W.D. Flanders, E.L. Frome, W.G. Tankersley, and S.A. Fry. (1988). Chemical exposures and central nervous system cancers: a case-control study among workers at two nuclear facilities. *Am J Ind Med* 13:351-362.

20. Chemfinder. (1998). *Beryllium CAS 7440-41-7*. http://www.chemfinder.camsoft.com/ (& type 7440-41-7), CambridgeSoft Corporation.

21. Cloudman, A.M., D. Vining, S. Barkulis, and J.J. Nickson. (1949). Bone changes observed following intravenous injections of beryllium (Abstract). *Am J Pathol* 25:810-811.

22. CRC. (1998). *Handbook of Chemistry and Physics.* Lide, D.R. and H.P.R. Frederikse, (eds.). New York, NY. CRC Press.

23. Crowley, J.F., J.G. Hamilton, and K.G. Scott. (1949). The metabolism of carrier-free radioberyllium in the rat. *J Biol Chem* 177:975-984.

24. Cullen, M.R., M.G. Chermiack, and J.R. Kominsky. (1986). Chronic beryllium disease in the United States. *Sem Respir Med* 7:203-209.

25. Cunningham, L. D. (1997). Beryllium. *U.S. Geological Survey; Minerals Information*. http://www.cdc.gov/niosh/.

26. Dean, J.A. (1992). *Lange's Handbook of Chemistry.* New York, NY. McGraw-Hill.

27. De Nardi, J.M., H.S. Van Ordstrand, G.H. Curtis, and J. Zielinski. (1953). Berylliosis — summary and survey of all clinical types observed in a 12-year period. *Arch Ind Hyg Occup Med* 8:1-24.

28. Dutra, F.R. and E.J. Largent. (1950). Osteosarcoma induced by beryllium oxide. *Am J Pathol* 26:197-209.

29. Dutra, F.R., E.J. Largent, and J.L. Roth. (1951). Osteogenic sarcoma after inhalation of beryllium oxide. *Arch Pathol* 51:473-479.

30. Dvivedi, N. and G. Shen. (1983). Beryllium toxicity in the laboratory processing of dental alloy. *J Dent Res* 62:232.

31. Eisenbud, M. (1993). Re: Lung cancer incidence among patients with beryllium disease. *J Natl Cancer Inst* 85(20):1697-1699.

32. Emsley, J. (1998). *The Elements*. Oxford. Clarendon Press. 34 pp.

33. Feldman, I., J.R. Havill, and W.F. Neuman. (1953). The state of beryllium in blood plasma. *Arch Biochem Biophys* 46:443-453.

34. Finch, G. L., Haley, P. J., Hoover, M. D., Griffith, W. C., Boecker, B. B., Mewhinney, J. A., and Cuddihy, R. G. (1990a). *Interactions between inhaled beryllium metal and plutonium dioxide in rats: effects on lung clearance.* Thomassen, D. G., Shyr, L. J., Bechtold, W. E., and Bradley, P. L. (eds). LMF-129, 125-128. Springfield, VA, National Technical Information Service. Inhalation Toxicology Research Institute Annual Report 1989-1990.

35. Finch, G.L., J.A. Mewhinney, M.D. Hoover, A.F. Eidson, P.J. Haley, and D.E. Bice. (1990b). Clearance, translocation, and excretion of beryllium following acute inhalation of beryllium oxide by beagle dogs. *Fundam Appl Toxicol* 15:231-241.

36. Finch, G. L., Haley, P. J., Hoover, M. D., Griffith, W. C., Boecker, B. B., Mewhinney, J. A., and Cuddihy, R. G. (1991). *Combined exposure of F344/N rats to beryllium metal and $^{239}PuO_2$ aerosols. IV.* Shyr, L. J., Finch, G. L., and Bradley, P. L. LMF-134, 99-102. Springfield, VA, National Technical Information Service. Inhalation Toxicology Research Institute Annual Report 1990-1991.

37. Finch, G.L., F.F. Hahn, W.C. Griffith, M.D. Hoover, W.W. Carlton, A.H. Rebar, J.A. Mewhinney, and R.G. Cuddihy. (1994a). F344 rat lung carcinogenicity from inhaled beryllium metal. *The Toxicologist* 14:264.

38. Finch, G. L., Hahn, F. F., Carlton, W. W., Rebar, A. H., Hoover, M. D., Griffith, W. C., Mewhinney, J. A., and Cuddihy, R. G. (1994b). *Combined exposure of F344 rats to beryllium metal and $^{239}PuO_2$ aerosols.* Belinsky, S. A., Hoover, M. D., and Bradley, P. L. (eds). ITRI-144, 77-80. Springfield, VA, National Technical Information Service. Inhalation Toxicology Research Institute Annual Report 1993-1994.

39. Finch, G.L., P.J. Haley, and M.D. Hoover. (1994c). Responses of rat lungs to low lung burdens of inhaled beryllium metal. *Inhal Toxicol* 6:205-224.

40. Finch, G.L., M.D. Hoover, F.F. Hahn, K.J. Nikula, S.A. Belinsky, P.J. Haley, and W.C. Griffith. (1996). Animal models of beryllium-induced lung disease. *Environ Health Perspect* 104(Suppl 5):973-979.

41. Finch, G.L., K.J. Nikula, and M.D. Hoover. (1998a). Dose-response relationships between inhaled beryllium metal and lung toxicity in C3H mice. *Toxicol Sci* 42:36-48.

42. Finch, G.L., T.H. March, F.F. Hahn, E.B. Barr, S.A. Belinsky, M.D. Hoover, J.F. Lechner, K.J. Nikula, and C.H. Hobbs. (1998b). Carcinogenic responses of transgenic heterozygous p53 knockout mice to inhaled $^{239}PuO_2$ or metallic beryllium [In Process Citation]. *Toxicol Pathol* 26:484-491.

43. Fodor, I. (1977). Histogenesis of beryllium-induced bone tumours. *Acta Morpho Acad Sci Hung* 25:99-105.

44. Furchner, J.E., C.R. Richmond, and J.E. London. (1973). Comparative metabolism of radionuclides in mammals. 8. Retention of beryllium in the mouse, rat, monkey and dog. *Health Phys* 24:293-300.

45. Gardner, L.U. and H.F. Heslington. (1946). Osteosarcoma form intravenous beryllium compounds in rabbits (Abstract). *Fed Proc* 5:221

46. Gilles, D. (1976). *Health Hazard Evaluation Determination.* Hardric Laboratories, Waltham, Mass. NIOSH Report No. HEE-76-103-349. Cincinnati, OH, National Institute for Occupational Safety and Health.

47. Gladney, E.S. and J.W. Owens. (1976). Beryllium emissions from a coal-fired power plant. *J Environ Sci Health* 11:297-311.

48. Grewal, D.S. and F.X. Kearns. (1977). A simple and rapid determination of small amounts of beryllium in urine by flameless atomic absorption. *At Absorpt Newsl* 16:131-132.

49. Groth, D.H., C. Kommineni, and G.R. MacKay. (1980). Carcinogenicity of beryllium hydroxide and alloys. *Environ Res* 21:63-84.

50. Haley, P.J., G.L. Finch, M.D. Hoover, and R.G. Cuddihy. (1990). The acute toxicity of inhaled beryllium metal in rats. *Fundam Appl Toxicol* 15:767-778.

51. Hayes, R.B. (1997). The carcinogenicity of metals in humans. *Cancer Causes Control* 8(3):371-385.

52. Hinds, M.W., L.N. Kolonel, and J. Lee. (1985). Application of a job—exposure matrix to a case-control study of lung cancer. *J Natl Cancer Inst* 75:193-197.

53. Hiruma, T. (1991). [Rabbit osteosarcoma induced by hydroxypropylcellulose mixed beryllium oxide pellet--comparison between implantations into bone marrow cavity and into fracture callus of the femur]. *Nippon Seikeigeka Gakkai Zasshi* 65:775-786.

54. Hoagland, M.G., R.S. Grier, and M.B. Hood. (1950). Beryllium and growth. I. Beryllium-induced osteogenic sarcomata. *Cancer Res* 10:629-635.

55. Hoover, M.D., G.L. Finch, and J.A. Mewhinney. (1990). Release of aerosols during sawing and milling of beryllium metal and beryllium alloys. *Appl Occup Environ Hyg* 5:787-791.

56. HSDB. (1997). *Hazardous Substance Data Bank.* National Library of Medicine Specialized Information Services. http://tomescps.com/assm.asp?HS6899

57. HSDB. (1998). *Hazardous Substance Data Bank*; National Library of Medicine Specialized Information Services. http://sis.nlm.nih.gov.

58. IARC. (1972). *Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds and Natural Products.* IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Man, Vol. 1, pp. 17-28. Lyon, France, World Health Organization.

59. IARC. (1980). *Some Metals and Metallic Compounds.* IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans. Vol 23, pp. 143-204. Lyon, France, World Health Organization.

60. IARC. (1987). *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Suppl. 7, pp. 127-128,139-142, 230-232, and 341-343. Lyon, France, World Health Organization.

61. IARC. (1993). *Beryllium, cadmium, mercury and exposures in the glass manufacturing industry.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France, World Health Organization 444 pp.

62. Infante, P.F., J.K. Wagoner, and N.L. Sprince. (1980). Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the Beryllium Case Registry. *Environ Res* 21:35-43.

63. Ishinishi, N., M. Mizunoe, T. Inamasu, and A. Hisanaga. (1980). Experimental study on carcinogenicity of beryllium oxide and arsenic trioxide to the lung of rats by an intratracheal instillation (Jpn.). *Fukuoka Igaku Zasshi* 71:19-26.

64. Iwan, G.R. (1987). Drinking water quality concerns of New York City, past and present. *Ann NY Acad Sci* 502:183-204.

65. Janes, J.M., G.M. Higgins, and J.F. Herrick. (1954). Beryllium-induced osteogenic sarcoma in rabbits. *J Bone Jt Surg* 36B:543-552.

66. Kelly, P.J., J.M. Janes, and L.F.A. Peterson. (1961). The effect of beryllium on bone. A morphological study of the progressive changes observed in rabbit bone. *J Bone Jt Surg* 43A:829-844.

67. Kleinman, M.T., W.J. Courtney, V.P. Guinn, T.C. Rains, J.R. Rhodes, and R.J. Thompson. (1989). General method for preparation of tissue samples for analysis for trace metals. *In: Methods of Air Sampling and Analysis.* J.P. Lodge, Jr., editor. Chelsea, MI. Lewis Publishers. pp. 619-622.

68. Klemperer, F.W., A.P. Martin, and J. Van Riper. (1951). Beryllium excretion in humans. *Arch Ind Hyg Occup Med* 4:251-260.

69. Klemperer, F.W., A.P. Martin, and R.E. Liddy. (1952). The fate of beryllium compounds in the rat. *Arch Biochem Biophys* 41:148-152.

70. Komitowski, D. (1968). Experimental beryllium-induced bone tumours as a model of osteogenic sarcoma (Pol.). *Chir Narzad Ruchu Ortop Pols* 33:237-242.

71. Komitowski, D. (1974). Beryllium-induced bone sarcomas (Ger.). *Verh Dtsch Ges Pathol* 58:438-440.

72. Kreiss, K., M.M. Mroz, L.S. Newman, J. Martyny, and B. Zhen. (1996). Machining risk of beryllium disease and sensitization with median exposures below 2g/m^3. *Am J Ind Med* 30:No-25.

73. Kriebel, D., N.L. Sprince, E.A. Eisen, and I.A. Greaves. (1988). Pulmonary function in beryllium workers: assessment of exposure. *Br J Ind Med* 45:83-92.

74. Kuroda, K., G. Endo, A. Okamoto, Y.S. Yoo, and S. Horiguchi. (1991). Genotoxicity of beryllium, gallium and antimony in short-term assays. *Mutat Res* 264:163-170.

75. Lansdown, A.B.G. (1995). Physiological and toxicological changes in the skin resulting from the action and interaction of metal ions. *Crit Rev Toxicol* 25(5):397-462.

76. Larramendy, M.L., N.C. Popescu, and J.A. DiPaolo. (1981). Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. *Environ Mutag* 3:597-606.

77. Leonard, A. and A. Bernard. (1993). Biomonitoring exposure to metal compounds with carcinogenic properties. *Environ Health Perspect* 101(Suppl 3):127-133.

78. Leonard, A., and R. Lauwerys. (1987). Mutagenicity, carcinogenicity and teratogenicity of beryllium. *Mutat Res* 186:35-42.

79. Levi-Setti, R., J.P. Berry, J.M. Chabala, and P. Galle. (1988). Selective intracellular beryllium localization in rat tissue by mass-resolved ion microprobe imaging. *Biol Cell* 63:77-82.

80. Lewis, F. A. (1980). *Health Hazard Evaluation Determination Report.* Bertoia Studio, Bally, Pennsylvania. NIOSH Report No. HE-79-78-655. Cincinnati, OH, National Institute for Occupational Safety and Health.

81. Litvinov, N.N., V.F. Kazenashev, and P.F. Bugryshev. (1983). Blastomogenic activities of various beryllium compounds. (Russ.). *Eksp Onkol* 5:23-26.

82. Litvinov, N.N., V.A. Popov, T.V. Vorozheikina, V.F. Kazenashev, and P.F. Bugryshev. (1984). Materials to specify MAC for beryllium in the work environment (Russ.) *Gig Tr Prof Zabol* 1:34-37.

83. LLNL. (1997). http://www-training.llnl.gov/wbt/hc/Be/Examples.html.

84. Loomis, D.P. and S.H. Wolf. (1996). Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947-1990 [see comments]. *Am J Ind Med* 29:131-141.

85. MacMahon, B. (1994). The epidemiological evidence on the carcinogenicity of beryllium in humans. *J Occup Med* 36:15-24.

86. Magos, L. (1991). Epidemiological and experimental aspects of metal carcinogenesis-Physicochemical properties, kinetics, and the active species. *Environ Health Perspect* 95:157-189.

87. Mancuso, T.F. (1979). *Occupational lung cancer among beryllium workers,* In: Dusts and Disease. Pathotox Publishers, Park Forest, IL. 463 pp.

88. Mancuso, T.F. (1980). Mortality study of beryllium industry workers' occupational lung cancer. *Environ Res* 21:48-55.

89. Matsuura, K. (1974). Experimental studies on the production of osteosarcoma by beryllium compounds, and the effects of irradiation (Jpn.). *Jpn J Orthop Assoc* 48:403-418.

90. Mazabraud, A. (1975). [Experimental production of bone sarcomas in the rabbit by a single local injection of beryllium] Production experimentale de sarcomes osseux chez le lapin par injection unique locale de Beryllium. *Bull Cancer* 62:49-58.

91. Meyer, K.C. (1994). Beryllium and lung disease. *Chest* 106:942-946.

92. Nesnow, S., L.L. Triplett, T.J. Slaga. (1985). Studies on the tumor initiating, tumor promoting, and tumor co-initiating properties of respiratory carcinogens. *Carcin Comp Surv* 8:257-277.

93. Nickell-Brady C., F.F. Hahn, G.L. Finch, and S.A. Belinsky. (1994). Analysis of K-ras, p53 and c-raf-1 mutations in beryllium-induced rat lung tumors. *Carcinogenesis* 15:257-262.

94. Nikula, K. J., Belinsky, S. A., Hoover, M. D., and Finch, G. L. (1994). *Comparative pulmonary carcinogenicity of inhaled beryllium in A/J and C3H/HeJ mice.* S.A. Belinsky, Hoover, M. D., and Bradley, P. L. (eds.) ITRI-144, 81-83. Springfield, VA, National Technical Information Service. Inhalation Toxicology Research Institute Annual Report 1993-1994.

95. NIOSH. (1976). *National Institute for Occupational Safety and Health. National Occupational Hazard Survey (1972-74).* Cincinnati, OH, Department of Health, Education, and Welfare.

96. NIOSH. (1984). *National Institute for Occupational Safety and Health. National Occupational Exposure Survey (1980-83).* Cincinnati, OH, Department of Health and Human Services.

97. OSHA. (1989). *personal communication* (as cited in WHO 1990).

98. Parker, V.H. and C. Stevens. (1979). Binding of beryllium to nuclear acidic proteins. *Chem Biol Interact* 26:167-177.

99. Paschal, D.C. and G.G. Bailey. (1986). Determination of beryllium in urine with electrothermal atomic absorption using the L'vov platform and matrix modification. *At Spectrosc* 7:1-3.

100. Paton, G.R. and A.C. Allison. (1972). Chromosome damage in human cell cultures induced by metal salts. *Mutat Res* 16:332-336.

101. Reeves, A.L., D. Deitch, and A.J. Vorwald. (1967). Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. *Cancer Res* 27:439-445.

102. Reeves, A.L. and A.J. Vorwald. (1967). Beryllium carcinogenesis. II. Pulmonary deposition and clearance of inhaled beryllium sulfate in the rat. *Cancer Res* 27:446-451.

103. Rooney, C., V. Beral, N. Maconochie, P. Fraser, and G. Davies. (1993). Case-control study of prostatic cancer in employees of the United Kingdom Atomic Energy Authority. *BMJ* 307:1391-1397.

104. Rosenkranz, H.S. and L.A. Poirier. (1979). Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and non-carcinogens in microbial systems. *J Natl Cancer Inst* 62:873-891.

105. Rossman, M.D., O.P. Preuss, and M.B. Powers. 1991. *Beryllium: Biomedical and Environmental Aspects.* Baltimore, MD, U.S.A. Williams and Wilkins.

106. Saracci, R. (1991). Beryllium and lung-cancer – adding another piece to the puzzle of epidemiologic evidence. *J Natl Cancer Inst* 83(19):1362-1363.

107. Sathiakumar, N., E. Delzell, Y. Amoateng-Adjepong, R. Larson, and P. Cole. (1997). Epidemiologic evidence on the relationship between mists containing sulfuric acid and respiratory tract cancer. *Crit Rev Toxicol* 27(3):233-251.

108. Sax, N.I. and R.J. Lewis, Sr. (1987). *Hawleys Condensed Chemical Dictionary, 11th Ed.,* New York. VanNostrand Reinhold.

109. Schepers, G.W.H., T.M. Durkan, A.B. Delehant, and F.T. Creedon. (1957). The biological action of inhaled beryllium sulfate. *Arch Ind Health* 15:32-58.

110. Schroeder, H.A. and M. Mitchener. (1975). Life-term studies in rats: effects of aluminum, barium, beryllium and tungsten. *J Nutr* 105(4):421-427.

111. Scott, J.K., W.F. Neuman, and R. Allen. (1950). The effect of added carrier on the distribution and excretion of soluble 7Be. *J Biol Chem* 182:291-298.

112. Simmon, V.F. (1979). In vitro mutagenicity assays of chemical carcinogens and related compounds with Salmonella typhimurium. *J Natl Cancer Inst* 62:893-899.

113. Simmon, V.F., H.S. Rosenkranz, E. Zeiger, and L.A. Poirier. (1979). Mutagenic activity of chemical carcinogens and related compounds in the intraperitoneal host-mediated assay. *J Natl Cancer Inst* 62:911-918.

114. Skilleter, D.N. and R.J. Price. (1984). Lymphocyte beryllium binding: relationship to development of delayed beryllium sensitivity. *Int Arch Allergy Appl Immunol* 73:181-183.

115. Snow, E.T. (1992). Metal carcinogenesis: mechanistic implications. *Pharmacol Ther* 53:31-65.

116. Sprince, N.L., H. Kazemi, and H.L. Hardy. (1976). Current (1975) problem of differentiating between beryllium disease and sarcoidosis. *Ann NY Acad Sci* 278:654-664.

117. Steenland, K. and E. Ward. (1991). Lung cancer incidence among patients with beryllium disease: a cohort mortality study [see comments]. *J Natl Cancer Inst* 83:1380-1385.

118. Stange, A.W., D.E. Hilmas, and F.J. Furman. (1996). Possible health risks from low level exposure to beryllium. *Toxicology* 111:213-224.

119. Steenland, K., D. Loomis, C. Shy, and N. Simonsen. (1996). Review of occupational lung carcinogens. *Am J Ind Med* 29:474-490.

120. Stiefel, T., K. Schulze, H. Zorn, and G. Tolg. (1980). Toxicokinetic and toxicodynamic studies of beryllium. *Arch Toxicol* 45:81-92.

121. Tapp, E. (1966). Beryllium induced sarcomas in the rabbit tibia. *Br J Cancer* 20:778-783.

122. Tapp, E. (1969). Osteogenic sarcoma in rabbits following subperiosteal implantation of beryllium. *Arch Pathol* 88:89-95.

123. TRI. (1996). http://toxnet.nlm.nih.gov/servlets/simple-search?1.15.1.2358.

124. Tsalev, D.L. and Z.K. Zaprianov, eds. (1984). *Atomic absorption spectrometry in occupational and environmental health practice.* Boca Raton, FL, CRC Press, pp. 96-100, 27-29.

125. Tso, W.W. and W.P. Fung. (1981). Mutagenicity of metallic cations. *Toxicol Lett* 8:195-200.

126. U.S. DOE. (1999). *About Beryllium.* http://tis.eh.doe.gov/be/webdoc1.html-ssi, Washington, DC. U.S. Department of Energy.

127. U.S. EPA. (1980). *Ambient water quality criteria for beryllium.* EPA-440/5-80-024. Washington, DC, Office of Water Regulations and Standards, Criteria and Standards Division, U.S. Environmental Protection Agency.

128. U.S. EPA. (1986a). *Method 6010. Inductively coupled plasma atomic emission spectroscopy.* In: Test Methods for Evaluating Solid Waste—Physical/Chemical Methods, 3rd Ed., Vol 1A (U.S. EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 6010-1-6010-17.

129. U.S. EPA. (1986b). *Method 7090. Beryllium (atomic absorption, direct aspiration).* In: Test Methods for Evaluating Solid Waste—Physical/Chemical Methods, 3rd Ed., Vol 1A (U.S. EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 7090-1-7090-3.

130. U.S. EPA. (1986c). Method 7091. *Beryllium (atomic absorption, furnace technique).* In: Test Methods for Evaluating Solid Waste—Physical/Chemical Methods, 3rd Ed., Vol 1A (U.S. EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 7091-1-7091-3.

131. U.S. EPA. (1987). *Health Assessment Document for Beryllium (EPA Report No. 600/8-84-026F).* Research Triangle Park, NC. Office of Research and Development.

132. Vacher, J. and H.B. Stoner. (1968). The transport of beryllium in rat blood. *Biochem Pharmacol* 17:93-107.

133. Vainio, H. and J.M. Rice. (1997). Beryllium revisited [editorial; comment]. *J Occup Environ Med* 39:203-204.

134. Vorwald, A.J. (1967). The induction of experimental pulmonary cancer in the primate (Abstract I-07-e). Berlin, Germany. Springer. 125 pp.

135. Wagner, W.D., D.H. Groth, J.L. Holtz, G.E. Madden, and H.E. Stokinger. (1969). Comparative chronic inhalation toxicity of beryllium ores, bertrandite and beryl, with production of pulmonary tumors by beryl. *Toxicol Appl Pharmacol* 15:10-29.

136. Wagoner, J.K., P.F. Infante, and D.L. Bayliss. (1980). Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. *Environ Res* 21:15-34.

137. Ward, E., A. Okun, A. Ruder, M. Fingerhut, and K. Steenland. (1992). A mortality study of workers at seven beryllium processing plants. *Am J Ind Med* 22:885-904.

138. WebElements2000. (1999). *WebElements2000, the periodic table on the WWW*. http://www.webelements.com/ , England. Mark Winter, University of Sheffield.

139. WHO. (1990). *Environmental Health Criteria 106: Beryllium.* Geneva, World Health Organization.

140. Williams, W.J. (1996). United Kingdom Beryllium Registry: mortality and autopsy study. *Environ Health Perspect* 104(Suppl 5): 949-951.

141. Wing, S., C.M. Shy, J.L. Wood, S. Wolf, D.L. Cragle, W. Tankersley, and E.L. Frome. (1993). Job factors, radiation and cancer mortality at Oak Ridge National Laboratory: follow-up through 1984 [published erratum appears in Am J Ind Med (1993) 23: 673]. *Am J Ind Med* 23:265-279.

142. Witschi, H. (1968). Inhibition of deoxyribonucleic acid synthesis in regenerating rat liver by beryllium. *Lab Invest* 19(1):67-70.

143. Witschi, H.P. and W.N. Aldridge. (1968). Uptake, distribution and binding of beryllium to organelles of the rat liver cell. *Biochem J* 106:811-820.

144. Yamaguchi, S. (1963). Study of beryllium-induced osteogenic sarcoma (Jpn.). *Nagasaki Iggakai Zasshi* 38:127-138.

145. Yang, Y.W. and P. Coppens. (1978). The electron density and bonding in beryllium metal as studied by Fourier methods. *Acta Cryst* 34A:61

146. Zorn, H., T. Stiefel, and H. Diem. (1977). [The importance of beryllium and its compounds for the industrial physician-2. communication] Die Bedeutung des Berylliums und seiner Verbindungen fur den Arbeitsmediziner--2. Mitteilung. *Zentralbl Arbeitsmed Arbeitsschutz Prophyl* 27:83-88.

147. Zorn, H.R., T.W. Stiefel, J. Breuers, and R. Schlegelmilch. (1988). Beryllium. In: Seiler, H.G. and H. Sigel, eds, *Handbook on Toxicity of Inorganic Compounds*. New York, Marcel Deffer, pp. 105-114.

Appendix A: IARC. 1993. *Beryllium, Cadmium, Mercury and Exposures in the Glass Manufacturing Industry.* Monographs on the Evaluation of Carcinogenic Risks to Humans. Beryllium and Beryllium Compounds. World Health Organization. Lyon, France. Vol. 58, pp. A-1 – A-77.

Appendix B: Finch *et al.* (1996). Animal Models of Beryllium-induced Lung Disease. Environ Health Perspect 104(Suppl 5):B-1 – B-14.

Appendix C: Carcinogen Profile for Beryllium and Beryllium Compounds (NTP 8th Report on Carcinogens 1998) pp. C-1 – C-3.